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# Hypovolemic shock and resuscitation

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Hypovolemic shock and resuscitation

by

Piper Lynn Wall

A dissertation submitted to the graduate faculty  
in partial fulfillment of the requirements for the degree of  
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Ames, Iowa

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**ABSTRACT**

The long term goal of this research is to improve patient outcomes after hypovolemic shock by increasing our understanding of how patient and treatment variables affect outcome. In severely diarrheic calves (one cause of hypovolemic shock) the addition of the synthetic colloid 6% dextran 70 to the intravenous fluid resuscitation of affected calves was investigated. In this clinical, prospective study (10 control calves and 12 calves that received 10 ml/kg 6% dextran 70), no decrease in hospitalization or mortality (0 for both groups) was noted, suggesting 6% dextran 70 use in this setting would not be cost effective. In a rat hemorrhagic shock and resuscitation model, the association between gastrointestinal intraluminal  $\text{CO}_2$  partial pressure ( $\text{P}_i\text{CO}_2$ ) and outcome was investigated. An infrared air-flow based  $\text{P}_i\text{CO}_2$  monitoring system consisting of  $\text{CO}_2$  permeable (silicone) and impermeable (Teflon) tubing, and an end-tidal  $\text{CO}_2$  monitor was used. Male Wistar-Furth rats (23 without and 74 with an 18 hour pre-hemorrhage fast) were anesthetized, hemorrhaged ( $\text{MAP}=35\text{-}40\text{mmHg}$ ) for 90 minutes, and volume resuscitated ( $\text{MAP}\geq 80\text{mmHg}$ ) for 3 hours. Survivors were euthanized at 48 hours. In non-fasted rats, the start of resuscitation colon  $\text{P}_i\text{CO}_2$  was  $90 \pm 7$  mmHg in non-survivors and  $66 \pm 3$  mmHg in survivors ( $p < 0.01$ , two-way ANOVA for repeated values). The start of resuscitation base excess was  $-16.8 \pm 2.0$  mEq/l in non-survivors and  $-10.4 \pm 1.1$  mEq/l in survivors

( $p < 0.01$ , two-way ANOVA for repeated measures). The incidence of organ pathology was 0% lung, 26% liver, and 45% small intestine. Mortality was 35%. In the fasted rats, neither  $P_iCO_2$  nor base excess predicted mortality. (Start of resuscitation  $P_iCO_2$ : non-survivors,  $59 \pm 2$  mmHg; survivors,  $62 \pm 2$  mmHg. Start of resuscitation base excess: non-survivors,  $-14.4 \pm 0.6$  mEq/l; survivors  $-13.6 \pm 0.5$  mEq/l.) The incidence of organ pathology was 26% lung, 45% liver, and 85% small intestine ( $p < 0.05$  for each compared to non-fasted,  $\chi^2$ ). Mortality was 66% ( $p < 0.05$  compared to non-fasted,  $\chi^2$ ). Also, hypertonic saline dextran administration was 100% fatal in fasted rats.

## GENERAL INTRODUCTION

### Introduction

Hemorrhagic shock, a type of hypovolemic shock, is intimately linked with trauma. Trauma is the leading cause of death in the first four decades of life in the United States,<sup>1</sup> and multiple organ dysfunction syndrome (MODS) is the cause of most late (> 48 hours of hospitalization) trauma deaths.<sup>2</sup> Elevations in gastrointestinal intraluminal CO<sub>2</sub> partial pressure (P<sub>i</sub>CO<sub>2</sub>) have been shown to precede multiple organ dysfunction syndrome development and death in trauma<sup>3-5</sup> and other patients at risk<sup>6-8</sup> and, since decreased gastrointestinal mucosal energy status (ATP/ADP ratio) is believed to play a contributing role in the development of multiple organ dysfunction syndrome, the use of gastrointestinal intraluminal CO<sub>2</sub> partial pressure measurements in treatment algorithms is currently being explored.<sup>3,5</sup> (Elevations in gastrointestinal intraluminal CO<sub>2</sub> partial pressure that are not caused by increases in arterial PCO<sub>2</sub> are believed to be reflective of gastrointestinal mucosal ATP hydrolysis unmatched by mitochondrial ATP resynthesis.)

To determine whether improving the gastrointestinal mucosal energy status improves outcome, reproducible methods for assessing and improving gastrointestinal mucosal energy status must be developed. If the assumption that gastrointestinal intraluminal CO<sub>2</sub> partial pressure reflects mucosal energy status<sup>9-12</sup> is correct, then interventions that

decrease an elevated gastrointestinal intraluminal CO<sub>2</sub> partial pressure are improving mucosal energy status. The most clinically applicable types of interventions for use during patient resuscitation are cardiovascular interventions such as the intravenous administration of colloids and angiotensin converting enzyme inhibitors.

If inadequate gastrointestinal mucosal energy status plays an important initiating and potentiating role in the development of multiple organ dysfunction syndrome after trauma, timely application of interventions that improve gastrointestinal mucosal energy status should result in improvements in patient outcomes.

### **Dissertation Organization**

This dissertation consists of a collection of papers concerning various aspects of hypovolemic shock. The first paper, "Cost effectiveness of use of a solution of 6% dextran 70 in young calves with severe diarrhea," is a clinical study investigating the addition of 6% dextran 70, a synthetic colloid, to the resuscitative therapy for calves with severe diarrhea (one cause of hypovolemic shock). This paper is linked to the remainder of the dissertation in three ways: 1) the research involved a form of hypovolemic shock, 2) the effects of different types of resuscitative fluids were compared, and 3) indicators of shock severity were discussed. The second paper, "GI P<sub>i</sub>CO<sub>2</sub>: tissue specific monitoring for

improving patient outcomes," is a review of the theory behind gastrointestinal intraluminal CO<sub>2</sub> partial pressure monitoring and its potential clinical uses with an emphasis on potential veterinary applications. Hemorrhagic shock (a form of hypovolemic shock) appears to be an area where gastrointestinal intraluminal CO<sub>2</sub> partial pressure monitoring has great potential for helping to improve patient outcomes. The third paper, "A simple apparatus for frequent monitoring of gastrointestinal mucosal perfusion adequacy," describes a technique for monitoring gastrointestinal CO<sub>2</sub> partial pressure. The following two papers, "Colonic P<sub>i</sub>CO<sub>2</sub> and outcome during hemorrhagic shock and resuscitation in rats" and "Pre-hemorrhage fasting affects outcome and the predictive power of colonic P<sub>i</sub>CO<sub>2</sub> in rats," examine the relationship between colonic CO<sub>2</sub> partial pressure and outcome in a rat hemorrhagic shock and resuscitation model. The last paper, "Rapid administration of hypertonic saline dextran can cause respiratory compromise," describes the effects on outcome of rapid hypertonic saline dextran administration for resuscitation in the rat hemorrhagic shock model described in the sixth paper. Following the last paper, the General Conclusions section briefly summarizes the implications of the research results of the previous sections and discusses future research recommendations.

## Literature Review

### *Gastrointestinal $P_i\text{CO}_2$ and Mucosal Energy Status*

The work of Schlichtig and Bowles<sup>9</sup> and the reviews by Fiddian-Green<sup>10</sup> and by Gutierrez and Brown<sup>11</sup> show that increases in gastrointestinal  $P_i\text{CO}_2$  that are not caused by increases in arterial  $\text{PCO}_2$  are reflective of gastrointestinal mucosal ATP hydrolysis unmatched by ATP resynthesis by oxidative phosphorylation:  $\text{ATP} \rightarrow \text{ADP} + \text{P}_i + \text{H}^+$ ;  $\text{H}^+ + \text{HCO}_3^- \rightarrow \text{H}_2\text{CO}_3 \rightarrow \text{CO}_2 + \text{H}_2\text{O}$ . (See also article, "Protons and anaerobiosis", by Hochachka and Mommsen.<sup>12</sup>) Increases in  $P_i\text{CO}_2$  (or decreases in gastrointestinal  $\text{pH}_i$ , calculated using gastrointestinal  $P_i\text{CO}_2$ ) during hemorrhage<sup>13-25</sup> occur throughout the gastrointestinal tract<sup>14,15</sup> and generally coincide with decreases in mean arterial pressure (MAP),<sup>13,14,16-23,25</sup> cardiac output,<sup>14,16-18</sup> systemic oxygen delivery,<sup>15,17</sup> splanchnic oxygen delivery,<sup>18,19</sup> gastric blood flow,<sup>21</sup> GI mucosal perfusion,<sup>16</sup> mucosal capillary oxyhemoglobin saturation,<sup>23</sup> and gastrointestinal intraluminal  $\text{PO}_2$ .<sup>16,19</sup> During resuscitation, however, elevations in gastrointestinal  $P_i\text{CO}_2$  have been shown to exist in animals<sup>13,22</sup> and people<sup>3-5,26,27</sup> despite normal or greater than normal systemic cardiovascular indicators of resuscitation such as mean arterial pressure<sup>13,22</sup> and systemic oxygen delivery and consumption<sup>3-5,26</sup> and base deficit.<sup>5,27</sup> Additionally, in sepsis models,<sup>28,29</sup> mucosal acidosis<sup>28</sup> and increases in  $P_i\text{CO}_2$ <sup>29</sup> have been shown to occur despite normal to increased mucosal  $\text{PO}_2$ <sup>28</sup> and normal<sup>28</sup> to increased<sup>29</sup> mucosal perfusion (by laser-Doppler

flowmetry<sup>28</sup> and by microspheres<sup>29</sup>). Therefore, monitoring gastrointestinal  $P_i\text{CO}_2$ , not systemic cardiovascular variables or even intraluminal  $\text{PO}_2$ , is the current clinically appropriate method for monitoring gastrointestinal mucosal energy status. (<sup>31</sup>P magnetic resonance spectroscopy to directly monitor gastrointestinal mucosal energy status is theoretically possible but is currently not clinically available.<sup>30</sup>)

#### *Mucosal Energy Status and Outcome*

Increases in gastrointestinal  $P_i\text{CO}_2$  (or calculated decreases in gastrointestinal  $\text{pH}_i$ ) occur very early in humans during cardiovascular compromise<sup>24</sup> and, especially when persistent,<sup>3-5,31-35</sup> are strongly associated with multiple organ dysfunction syndrome<sup>3-5,26,27,32,35-39</sup> and death<sup>3-5,26,27,31-35,37-41</sup> in patients. (References 18-22 relate to trauma patients in particular.) Additionally, timely correction of gastrointestinal mucosal energy status, generally having been achieved by systemic cardiovascular interventions believed to increase mucosal perfusion, appears to have potential for improving patient outcomes.<sup>3,4,40</sup> These clinical data suggest that depletion of the energy stores in cells in the mucosal layer of the gastrointestinal tract contributes to the development of multiple organ dysfunction syndrome in patients. In a rabbit hepatoenteric ischemia/reperfusion multiple organ dysfunction syndrome model, increases in gastric intramucosal  $\text{H}^+$  concentration (calculated using  $P_i\text{CO}_2$ )

were shown to be significantly associated with increases in plasma alanine aminotransferase (indicating greater hepatic injury) and with increases in bronchoalveolar lavage protein (indicating greater pulmonary alveolar-capillary membrane injury).<sup>42</sup> A decrease in the gastric intramucosal H<sup>+</sup> concentration during reperfusion by inactivation of xanthine oxidase was associated with significantly less hepatic and pulmonary injury in this model. Whether a relationship between GI P<sub>i</sub>CO<sub>2</sub> and outcome similar to that reported in humans and rabbits exists in rat models of hemorrhage and resuscitation needs to be determined.

#### *Resuscitation Fluids*

Resuscitation from hemorrhage generally involves intravenously administered fluids, with lactated Ringer's being the most commonly used crystalloid and probably the most commonly used fluid overall. Resuscitation with intravenous lactated Ringer's, therefore, is commonly used as a standard against which to compare other therapies. Lactated Ringer's is isosmotic and inexpensive; however, approximately 80% of the administered fluid leaves the vasculature within one hour.<sup>43</sup> This allows replacement of interstitial fluid losses but can make maintenance of adequate intravascular volume without achieving significant tissue edema difficult.<sup>44</sup> The use of 6% dextran 70, a synthetic colloid, in addition to lactated Ringer's for resuscitation should allow more rapid and prolonged increases in systemic O<sub>2</sub> delivery<sup>45</sup> since 6%



dextran 70 stays predominantly in the vascular compartment.<sup>44</sup> An additional possibly beneficial effect of dextran 70 is its ability to decrease neutrophil adhesiveness to endothelial cells,<sup>46,47,48</sup> thereby improving microvascular perfusion while potentially preventing some post-shock neutrophil mediated endothelial damage.<sup>46</sup> The addition of 6% dextran 70 to intravenous resuscitation protocols may, therefore, be one way to decrease an elevated GI  $P_iCO_2$  by simply improving systemic microvascular hemodynamics.<sup>45</sup>

#### *Angiotensin Converting Enzyme Inhibitors*

A pharmacologic cardiovascular intervention that may help decrease an elevated GI  $P_iCO_2$  by improving gastrointestinal microvascular perfusion is the addition of intravenous enalaprilat, an angiotensin converting enzyme inhibitor, to intravenous fluid resuscitation. Since angiotensin II appears to play a large role in the selective splanchnic vasoconstriction that occurs in shock,<sup>49-51</sup> investigating the use of enalaprilat to decrease GI  $P_iCO_2$  by decreasing splanchnic vasoconstriction is quite attractive. Enalaprilat has been shown to improve systemic oxygen delivery and consumption in trauma patients,<sup>52</sup> and its administration to fluid-loaded trauma patients converted a negative tissue oxygen challenge test to a positive one,<sup>53</sup> suggesting that enalaprilat improves microvascular hemodynamics beyond what is achieved with fluids alone. In surgical intensive care unit patients, continuous intravenous infusion of enalaprilat

resulted in decreased systemic vascular resistance, pulmonary capillary wedge pressure, and pulmonary artery pressure; greater systemic oxygen delivery, oxygen consumption, and oxygen extraction; and improvement in right ventricular ejection fraction as compared to the control group of patients.<sup>54</sup> In none of these three studies, however, was GI  $P_iCO_2$  reported. Decreases in ventricular ejection occur during hemorrhagic shock<sup>55,56</sup> and can persist during resuscitation.<sup>55-57</sup> Greater ventricular ejection fractions have been shown to be associated with both decreases in gastrointestinal  $P_iCO_2$  (pigs)<sup>58,59</sup> and greater patient survival.<sup>60</sup> In animal studies, angiotensin converting enzyme inhibitors have been shown to prevent increases in gastric vascular resistance<sup>49</sup> and to protect the gastric mucosa, increase small intestinal blood flow, and decrease systemic acidosis<sup>61</sup> in dog hemorrhagic shock models and to protect the intestinal mucosa in a rat mesenteric ischemia/reperfusion model.<sup>62</sup> Although gastrointestinal  $P_iCO_2$  was not monitored in these studies, decreased vascular resistance, increased blood flow, and mucosal protection would all be compatible with improvements in mucosal energy status.

In addition to improvements in mucosal perfusion by decreasing the formation of angiotensin II, enalaprilat may also improve general microvascular perfusion by increasing the half-life of bradykinin, thereby promoting endothelial production of nitric oxide (NO) and prostacyclin.<sup>63</sup>

Endothelial NO not only causes smooth muscle relaxation but also decreases neutrophil-endothelial adhesion independent of increases in venular wall shear rate.<sup>64</sup> Additionally, administration of nitroprusside, an NO donor, during resuscitation from hemorrhagic shock has been shown to result in a significant improvement in load independent ventricular function (increased ejection fraction).<sup>55</sup> Decreases in neutrophil-endothelial adhesion, increases in general microvascular perfusion, and improvements in ventricular function during resuscitation should be beneficial.

#### *Mucosal Energy Depletion to Multiple Organ Dysfunction Syndrome*

A general scheme to explain how unmatched ATP hydrolysis in cells in the mucosal layer of the gastrointestinal tract contributes to multiple organ dysfunction syndrome development follows: 1) cardiovascular compromise, 2) decrease in splanchnic perfusion<sup>16,18,19,21,23,65</sup> (at least partly mediated by angiotensin II<sup>49-51</sup>), 3) inadequate gastrointestinal mucosal oxygenation to support matching of ATP hydrolysis by ATP resynthesis via oxidative phosphorylation (results in increasing gastrointestinal  $P_iCO_2$ <sup>9-12</sup>) and inadequate oxygen partial pressure to support respiratory burst killing of bacteria by either enterocytes<sup>66</sup> or resident phagocytes (mucosal  $PO_2$  of 4 mm Hg has been reported for a rat hemorrhage and resuscitation model<sup>67</sup>), 4) increase in gastrointestinal permeability<sup>68-70</sup> and increase in bacterial and toxin

translocation,<sup>69,71-74</sup> 5) generation of proinflammatory cytokines<sup>72-75</sup> by enterocytes<sup>76</sup> and gut associated lymphoid tissue,<sup>72,75</sup> 6) priming<sup>77-80</sup> and increases in adhesiveness<sup>77,78</sup> of neutrophils (xanthine oxidase generation of  $O_2^-$  may be involved<sup>81</sup> as may platelet activating factor<sup>77-80,82</sup>), 7) promotion of and contribution to the systemic inflammatory response by proinflammatory cytokines<sup>72,83,84</sup> and primed<sup>81,82</sup> and sticky<sup>85,86</sup> neutrophils,<sup>77</sup> 8) failure of systemic resuscitative measures to restore adequate gastrointestinal mucosal ATP resynthesis by oxidative phosphorylation<sup>3-5,13,22,26,27</sup> continues to promote systemic inflammatory response,<sup>38</sup> and 9) development and progression of inflammatory organ damage and dysfunction (multiple organ dysfunction syndrome). (References 72, 77, and 78 are reviews that contributed substantially to the formulation of this model.)

#### *Neutrophil Adhesion*

CD11b/CD18 mediated neutrophil adhesion to endothelial cells is an important and possibly essential step in neutrophil mediated tissue damage.<sup>86-89</sup> Upregulation of the neutrophil CD11b/CD18 adhesion molecule<sup>77,85</sup> and decreased circulating numbers of neutrophils<sup>77</sup> have been shown to occur in trauma patients who subsequently develop MODS. Upregulation of neutrophil adhesion molecules has also been shown in animal models of shock<sup>90,91</sup> and MODS,<sup>78</sup> and blocking neutrophil adhesion with monoclonal antibodies<sup>87,91-95</sup> given intravenously shortly before or, more importantly, after

various insults has been shown to decrease tissue damage<sup>86,87,91-95</sup> and improve survival.<sup>93-95</sup> Whether the decreased GI mucosal energy status associated with hemorrhagic shock contributes to increases in neutrophil CD11b/CD18 expression, and how resuscitation interventions modulate such increases<sup>90</sup> should be evaluated.

One intervention in particular, the use of 6% dextran 70, deserves further mention. Intravenous administration of dextran 70 containing fluids after ischemia results in decreased neutrophil/endothelial cell interactions as compared to either lactated Ringer's or hetastarch (a synthetic colloid with slightly different structure but similar oncotic pressure).<sup>44,47</sup> The decreased adhesion might be the result of direct coating of CD11b/CD18 or other adhesion molecules on neutrophils (e.g. L-selectin) or endothelial cells (e.g. P-selectin or ICAM-1) or may be caused by interference with a priming stimulus.

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**COST EFFECTIVENESS OF USE OF A SOLUTION OF 6% DEXTRAN 70 IN  
YOUNG CALVES WITH SEVERE DIARRHEA**

A paper published in J Am Vet Med Assoc<sup>1</sup>

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**Abstract**

**Objective-**To determine whether intravenous administration of 6% dextran 70 solution to young calves with severe diarrhea is cost effective.

**Design-**Randomized, prospective, clinical trial.

**Animals-**22 calves < 2 months old that were hospitalized for diarrhea and that did not have pneumonia.

**Procedure-**All calves received antibiotics, were fed by use of an orogastric tube, were supplied with radiant heat, and were given crystalloids, IV, as deemed appropriate by an attending veterinarian. A group of 12 calves also received 500 ml of 6% dextran 70 solution, IV, over a 1-hour period as part of the initial treatment. Data were collected to determine whether early treatment with 6% dextran 70 solution resulted in a similar end cost for treatment because of a decrease in the volume of fluids administered IV, a decrease in the amount of time hospitalized, or a decrease in mortality.

**Results-**Capillary refill times, heart rates, respiratory rates, and rectal temperatures; and scores for dehydration,

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mucous membrane color, lung sounds, mental status, and suckling response, were not different between the 2 groups of calves at admission. Differences were not detected in client charges or in hospitalized time (6% dextran 70 group, \$89.68  $\pm$  11.05 and 36  $\pm$  3 hours; control group, \$88.02  $\pm$  4.93 and 36  $\pm$  4 hours), but those charges did not include costs for the 6% dextran 70 solution.

**Clinical Implications**-Use of 6% dextran 70 solution as part of the resuscitation of most young calves with diarrhea requiring hospitalization is not likely to be cost effective. (*J Am Vet Med Assoc* 1996;209:1714-1715)

## Introduction

Accounting for approximately one fourth of all new disease in cow-calf operations, calf diarrhea is a substantial problem for cattle producers.<sup>1</sup> Therefore, a change in treatment of severely affected calves that would result in a decrease in treatment costs by decreasing the duration of hospitalization, amount of antibiotics administered, or calf mortality, would be beneficial. The general clinical state of diarrheic calves (moderate-to-severe dehydration, lack of mental alertness, pale mucous membranes) and their response to crystalloids administered intravenously made it reasonable to test the use of 6% dextran 70 solution, a commercially available synthetic colloid solution, as part of the initial resuscitation protocol for diarrheic calves requiring

hospitalization. Improvements in calf outcomes might be expected with the use of 6% dextran 70 solution administered IV, because it holds fluid in the vascular system much better than crystalloids, thereby providing better systemic oxygen delivery as well as less tissue edema<sup>2</sup>; it maintains or increases intravascular oncotic pressure, which may aid fluid absorption from the gastrointestinal tract; and it decreases neutrophil/endothelial interactions in the microvasculature, leading to better microvascular flow and, possibly, less undesirable neutrophil priming.<sup>3,4</sup> To determine if these properties make the use of 6% dextran 70 solution cost effective in treating diarrheic calves, a randomized, prospective, clinical trial was conducted.

### **Materials and Methods**

During April to June of 1994 and 1995, calves < 2 months old admitted with diarrhea sufficiently severe to require hospitalization and treatment with fluids, IV, were randomly assigned to the 6% dextran 70 group or the control group. Randomization was done by drawing slips of paper labeled "6% dextran 70" or "control" from a box. Calves in the 6% dextran 70 group received 500 ml of 6% dextran 70 solution,<sup>a</sup> IV, as part of their initial (first hour) fluid resuscitation. Calves in both groups received crystalloid solution intravenously,<sup>b</sup> antibiotics, were fed milk or other nutritional products via an orogastric tube,<sup>c,d</sup> and were

supplied radiant heat as deemed necessary by an attending veterinarian. Calves were discharged from the clinic when they were alert, could stand unaided, and did not require additional hospital care such as radiant heat and intravenously administered fluids.

Capillary refill time, heart rate, respiratory rate, and rectal temperature; and scores for dehydration, mucous membrane color, lung sounds, mental status, and suckling response were collected at the initial examination and every 12 hours thereafter. Scores were assigned for dehydration (1 = dehydration not apparent, 2 = mild dehydration as indicated by slight increase in skin tenting, 3 = moderate dehydration as indicated by increase in skin tenting and eyes somewhat sunken into the head, and 4 = severe dehydration as indicated by increase in skin tenting and eyes extremely sunken into head), mucous membrane color (1 = pink, normal colored mucous membranes, 2 = pale mucous membranes, and 3 = gray to white mucous membranes), lung sounds (1 = normal lung sounds, 2 = increased lung sounds), mental status (1 = alert appearance, 2 = calf did not appear aware of its environment, but was responsive to physical stimuli such as injections, and 3 = calf was not responsive to physical stimuli), and suckling response (1 = any attempt by the calf to suckle on a finger placed in its mouth, 2 = suckling response was lacking). An attempt was also made to evaluate the volume and fluid consistency of the diarrhea; however, this proved to be

impractical and not useful.

Differences between pairs of mean values were assessed for significance, using Student's *t*-test. Differences were considered significant at a value of  $P < 0.05$ .

## Results

One calf that received 250 ml of 6% dextran 70 solution was removed from the study reported here because diarrhea was not observed while the calf was in the clinic, and the calf, which died 30 minutes after initial examination, had severe pneumonia that was detected during necropsy. All of the other calves recovered and were discharged from the hospital.

On the basis of the measured variables, differences in severity at initial examination were not evident between the 2 groups of calves (Table 1). Weights and ages of the calves in the 2 groups also were similar (mean  $\pm$  SE; 6% dextran 70 group  $42 \pm 3$  kg and  $17 \pm 7$  days; control group,  $48 \pm 2$  kg and  $11 \pm 2$  days). The volume of fluid administered, IV, per calf (6% dextran 70 group,  $8.4 \pm 1.2$  L; control group,  $10.3 \pm 1.0$  L), client charges per calf (6% dextran 70 group,  $\$89.68 \pm 11.05$ ; control group,  $\$88.02 \pm 4.93$ ), and hospitalized time per calf (6% dextran 70 group,  $36 \pm 3$  hours; control group,  $36 \pm 4$  hours) were not different. Clients were not charged for the 6% dextran 70 solution; however, had such charges been included, the cost to treat calves in the 6% dextran 70 group would have been increased by  $\$39.95$  per calf.



## Discussion

As compared to resuscitation protocols in which crystalloid solutions were the only fluids administered intravenously, the administration of 6% dextran 70 solution, IV, as part of the initial resuscitation protocol for diarrheic calves requiring hospitalization has several theoretic benefits, including better vascular volume support and systemic oxygen delivery, less tissue edema, maintenance or improvement of intravascular oncotic pressure, and improved microvascular perfusion.<sup>2-4</sup> The 6% dextran 70 solution, however, was more expensive than commercially available crystalloid solutions. Therefore, to be clinically useful in the treatment of diarrhea of calves, the theoretic benefits of the use of 6% dextran 70 solution would need to translate to substantial improvements in clinical outcomes over those obtained without its use. Such improvements were not detected in our study, leading to the conclusion that the use of 6% dextran 70 solution in the resuscitation of most diarrheic calves is not likely to be cost effective (ie, less expensive than, but at least as effective as, alternative treatments, or more expensive than alternative treatments, but with additional benefits worth the additional cost).<sup>5,6</sup>

Some limitations of the study reported here should be kept in mind. The assessments of severity (eg, capillary refill time) were performed not on the basis of mortality predictive value, but on the basis that they could be done at

no cost (hospital staff time was donated for this study) and that they also could be performed in any other veterinary clinic or hospital. If sensitive and specific predictors of mortality for severely diarrheic calves are developed and used for stratification, the administration of 6% dextran 70 solution intravenously might prove beneficial in a group of calves at high risk for mortality. Use of a higher dosage of 6% dextran 70 solution, although adding expense, also might be more efficacious in promoting and maintaining good microvascular perfusion. Such a dosage might be warranted in a calf at high risk, particularly when it is a calf with great economic value.

#### Footnotes

- <sup>a</sup> 6% Gentran 70, McGaw, Irvine, CA.
- <sup>b</sup> Multisol-R, Sanofi Animal Health, Overland Park, KS.
- <sup>c</sup> Protec, C & G Products, Carroll, IA.
- <sup>d</sup> Replenish, TechAmerica, Fermenta Animal Health Co., Kansas City, MO.

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**Table 1.** Clinical assessments of diarrheic calves at initial examination.

Variable	Treatment group	
	6% dextran 70 calves	Control calves
Capillary refill time (s)	2.5 $\pm$ .2	2.3 $\pm$ .2
Heart rate (beats per min)	104 $\pm$ 7	114 $\pm$ 5
Respiratory rate (breaths per min)	26 $\pm$ 3	27 $\pm$ 2
Rectal temperature ( $^{\circ}$ C)	36.7 $\pm$ .6	37.8 $\pm$ .6
Dehydration status	3.3 $\pm$ .2	2.8 $\pm$ .1
Mucous membrane color	1.7 $\pm$ .6	2.0 $\pm$ .1
Lung sounds	1.8 $\pm$ .1	2.0 $\pm$ 0
Mental status	2.4 $\pm$ .2	2.2 $\pm$ .2
Sucking response	1.2 $\pm$ .1	1.4 $\pm$ .2

\* Values reported are mean  $\pm$  SEM.

**GI  $P_i\text{CO}_2$ : TISSUE SPECIFIC MONITORING FOR IMPROVING PATIENT  
OUTCOMES**

A paper published in the J Vet Emerg Crit Care<sup>1</sup>

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**Summary**

Improvements in human patient monitoring, despite development in animals, do not always find their way into veterinary clinical use because of financial constraints. Gastrointestinal intraluminal  $\text{CO}_2$  partial pressure (GI  $P_i\text{CO}_2$ ) monitoring, however, is not only proving very beneficial in human trauma and critical patient care but is also very likely to become relatively inexpensive. By providing information on the perfusion adequacy of a high risk, critically important tissue, the GI mucosa, GI  $P_i\text{CO}_2$  monitoring offers an easily accessible indicator of the efficacy and adequacy of resuscitative interventions. The potential for decreasing morbidity and mortality is enormous. Therefore, the practicing veterinarian should become familiar with GI  $P_i\text{CO}_2$  monitoring theory and technology so he or she can be better prepared to incorporate it into practice when it becomes available.

**Key Words:** gastrointestinal tonometry, shock, resuscitation,

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monitoring, outcome prediction

## Introduction

"The failure to achieve optimal resuscitation is due to the failure of conventional measurements of tissue oxygenation to identify inadequately treated shock."<sup>1</sup> In addition to financial inaccessibility for many of our veterinary patients, global measurements of oxygen delivery, consumption, and extraction simply do not provide reliable information on the adequacy of tissue oxygenation and energy status.<sup>1-14</sup> Due to this lack of tissue sensitivity of systemic measurements, the use of gastrointestinal intraluminal CO<sub>2</sub> partial pressure (GI P<sub>i</sub>CO<sub>2</sub>) monitoring is increasing in human medicine.<sup>4-9,12,14-22</sup> Measurements of the GI P<sub>i</sub>CO<sub>2</sub> reflect the energy status of the GI mucosa, a tissue at high risk for inadequate perfusion during shock and resuscitation. This approach to patient monitoring is likely to become affordable for veterinary patients, and it has great potential for decreasing veterinary emergency and critical care patient morbidity and mortality as well as helping to predict complications and necessary interventions.

## Theoretical Basis

The relationship between GI P<sub>i</sub>CO<sub>2</sub> and the adequacy of GI mucosal ATP has been fully described in an excellent review by Fiddian-Green<sup>23</sup> and is shown by the following equations: ATP →

$\text{ADP} + \text{P}_i + \text{H}^+; \text{H}^+ + \text{HCO}_3^- \rightarrow \text{H}_2\text{CO}_3 \rightarrow \text{CO}_2 + \text{H}_2\text{O}$ . Since  $\text{CO}_2$  is freely diffusible, GI  $\text{P}_i\text{CO}_2$  increases as mucosal ATP is depleted and decreases when therapy restores an appropriate mucosal cellular ratio of ATP hydrolysis to ATP resynthesis by oxidative phosphorylation.<sup>23-26</sup> GI  $\text{P}_i\text{CO}_2$ , by reflecting mucosal cellular energy status, indicates the adequacy of mucosal perfusion irrespective of the actual GI mucosal microvascular flow and the mucosal  $\text{PO}_2$ .

The approximate GI  $\text{pH}_i$  can be calculated from the GI  $\text{P}_i\text{CO}_2$  and the arterial bicarbonate,<sup>23</sup> and this calculated value is, in fact, commonly reported. Obtaining arterial bicarbonate measurements, however, adds to the cost of patient care and generally involves the removal of blood from the patient - a commodity of which our patients have a limited supply. Fortunately, the directly measured GI  $\text{P}_i\text{CO}_2$  better reflects the adequacy of mucosal perfusion<sup>27-29</sup> and is a more specific predictor of mortality than the calculated GI  $\text{pH}_i$ .<sup>17</sup> Therefore, the additional cost as well as the undesirable blood withdrawal needed for calculating the GI  $\text{pH}_i$  appear unnecessary.

### Patient Relevance

GI  $\text{P}_i\text{CO}_2$  monitoring provides an indication of energy status of one of the first regions of the body, the GI mucosa, to be adversely affected in shock.<sup>2,3,8,10,22,23,30-35</sup> Furthermore, this tissue commonly remains under-resuscitated despite the

appearance of adequate patient resuscitation as measured by systemic indices.<sup>1,4-6,9,10,14,19,30,36,37</sup> In fact, GI  $P_iCO_2$  is an earlier and more sensitive predictor of complications and death than such systemic indicators as blood pressure, arterial lactate, oxygen delivery, and oxygen consumption.<sup>4,6,12,14-20</sup> Considering the metabolic demands of the GI mucosal cells, the contribution of the vast numbers of T and B cells present in the gut associated lymphoid tissue to overall immunity,<sup>38</sup> the probable body defense relevance of the bactericidal activities of GI mucosal cells,<sup>39</sup> the toxic nature of many of the GI luminal contents, the impressive ability of the GI system to generate proinflammatory cytokines<sup>40,41</sup> and to prime neutrophils,<sup>41-43</sup> and the combined improvement in GI perfusion<sup>44-46</sup> and reduction in septic complications<sup>47-49</sup> with early enteral feeding, it is not surprising that a large body of both basic and clinical research strongly implicates inadequate GI mucosal perfusion in the development of multiple organ dysfunction syndrome (MODS).<sup>4,6,12,14-22,33,40-43,50-54</sup>

Fortunately, GI  $P_iCO_2$  monitoring is clinically available to assess the adequacy of GI mucosal perfusion in patients. Human clinical trials have demonstrated improved patient outcomes when interventions prevented a low GI  $pH_i$  (high GI  $P_iCO_2$ ) from developing and/or persisting.<sup>18,21</sup> In fact, the prevention of inadequate GI mucosal perfusion during cardiac surgery through the preemptive use of perioperative plasma volume expansion with colloid (6% hydroxyethyl starch)



resulted in a reduced incidence not only of major complications but also of minor complications such as disorientation, dyspnea, wound infection, and persistent nausea and vomiting.<sup>21</sup> Additionally, in a prospective randomized trial using GI  $pH_i$  monitoring to assess the adequacy of resuscitation of trauma patients, decreases in GI  $pH_i$  provided the earliest warning of systemic complications including bacteremia, intra-abdominal hypertension, intestinal anastomotic leak, intestinal gangrene or pregangrene, and intra-abdominal abscess.<sup>6</sup> The provision of an early indicator of a developing problem inside the patient led to several successful interventions.<sup>6</sup> A persistently low GI  $pH_i$  (high GI  $P_iCO_2$ ) was the first abnormal sign in all the nonsurvivors, and the time for optimization of GI  $pH_i$  was significantly longer in nonsurvivors than survivors.<sup>6</sup> The results of these trials combined with those of a study by Bjorck and Hedberg<sup>16</sup> lead to several conclusions: (1) inadequate GI mucosal perfusion can be prevented; (2) prevention is associated with improved outcomes; (3) complete early resuscitation is extremely important; (4) continuous GI  $P_iCO_2$  trending for assessing both the adequacy of patient resuscitation and the efficacy of different resuscitative interventions for each patient has great potential for improving outcomes; (5) there is an interplay between both the degree and the duration of the inadequate mucosal perfusion in determining outcome; (6) patient GI mucosal status should be evaluated and dealt with

early.

#### Where To Measure GI $P_iCO_2$

In the majority of reported human clinical trials, GI  $P_iCO_2$  has been monitored in the stomach.<sup>4-9,12,13,15-21</sup> Colon GI  $P_iCO_2$  monitoring, however, appears to be an even better technique for assessing current and predicting future patient status.<sup>16,34</sup> The small intestine, though less accessible, is also an acceptable site for  $P_iCO_2$  monitoring.<sup>10,29,30,34,55,56</sup> In addition, changes in esophageal<sup>57</sup> and rectal<sup>56</sup>  $P_iCO_2$  and directly measured rectal  $pH_i$ <sup>58</sup> have now been shown to correlate with changes in gastric and ileal  $P_iCO_2$ . Considering its easy accessibility, the rectum would therefore appear to be an excellent  $P_iCO_2$  monitoring site.

#### Technology

The currently commercially available product for measuring GI  $P_iCO_2$  (Tonometrics Tonometer<sup>®</sup>) is a modified nasogastric tube with a silicone balloon on the end. Placement of the silicone balloon in the GI tract is followed by filling the balloon with 2.5 ml of saline, waiting at least 20 minutes for sample equilibration, withdrawing the sample, and measuring the  $PCO_2$  of the saline with a blood-gas analyzer. The need for a blood-gas analyzer, a somewhat expensive piece of equipment that is generally not particularly accurate for measuring the  $PCO_2$  of saline,<sup>59,60</sup> and

the relatively long lag time between readings make this methodology less than ideal.

To provide continuous GI  $P_iCO_2$  monitoring capability with very little lag time (less than 2 minutes<sup>61</sup> and less than 5 minutes<sup>62</sup>), at least two air-flow driven  $PCO_2$  monitoring systems have been reported.<sup>61,62</sup> Both systems use an external infrared  $CO_2$  sensor to measure the  $PCO_2$  of air which has passed through  $CO_2$  permeable tubing that was placed in the portion of the GI tract of interest (colon,<sup>61</sup> stomach<sup>62</sup>). Continuous  $PCO_2$  measurement in air using an infrared  $CO_2$  sensor has several advantages: such a system potentially decreases the cost of  $P_iCO_2$  monitoring since neither reagents nor blood-gas analyzer cartridges are consumed; it allows sudden changes in GI mucosal status to be detected without the sample averaging effects of a long equilibration; it provides continuous real-time trending for bed-side patient status assessment; and it offers the potential to rapidly evaluate the efficacy of different resuscitative interventions (e.g. fluids, cardiovascular drugs, enteral therapy) for each patient.

At this time, we are developing a new real-time continuous bed-side infrared GI  $P_iCO_2$  monitoring system that does not require air-flow. A relatively small (.2 cm diameter by 2.5 cm long), reflectorized  $CO_2$  permeable chamber is connected to an infrared light emitting diode and an infrared detector by fluoride optical fibers so that the only lag time involved is for  $CO_2$  diffusion in and out of the  $CO_2$  permeable

chamber. Involving no consumable parts, this type of monitor should eventually be in the price range of pulse oximetry (unpublished observation).

An alternate possibility for clinical use is monitoring of rectal  $pH_i$  rather than rectal  $P_iCO_2$ . Continuous measurement of rectal  $pH_i$  has been done in pigs using an available standard glass body pH electrode (Semi-Micro Combination electrode, Catalog No. 476540, Corning Products, Corning, NY).<sup>58</sup>

### **Veterinary Use**

Already investigated in dogs as well as pigs, rats, and humans, GI  $P_iCO_2$  monitoring has enormous potential for improving veterinary patient care, especially trauma and gastric dilatation and volvulus patients. It offers (1) a superior method for assessing shock severity, (2) a method for monitoring treatment efficacy that allows patient tailoring of interventions to optimize patient outcomes, (3) an early warning system for problems (e.g. anastomotic leak) so that they can be quickly corrected, and (4) a possible predictor of survival and of complications. In regard to this last point, the ability to predict what supportive interventions may become necessary (e.g. prolonged ventilatory support, dialysis) should facilitate better informed veterinary and client decisions as to care and expenditure likely to be required for patient survival.

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**A SIMPLE APPARATUS FOR FREQUENT MONITORING OF GASTROINTESTINAL  
MUCOSAL PERFUSION ADEQUACY**

A paper submitted to Crit Care Med

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**ABSTRACT**

*Objective:* To test the in vitro accuracy and consistency of an end-tidal infrared CO<sub>2</sub> monitor and customized capnography tubing (modified feeding tube) based system designed to measure gastrointestinal intraluminal CO<sub>2</sub> partial pressure (an indicator of gastrointestinal mucosal perfusion adequacy).

*Design:* Controlled in vitro study.

*Setting:* Laboratory.

*Measurements and Main Results:* An end-tidal infrared CO<sub>2</sub> monitor was used to measure the CO<sub>2</sub> partial pressures of air samples from customized capnography tubes that were placed in a chamber containing either 5% CO<sub>2</sub>, 95% N<sub>2</sub> (PCO<sub>2</sub> 41 torr) or 10% CO<sub>2</sub>, 90% N<sub>2</sub> (PCO<sub>2</sub> 80 torr). Samples were taken at discrete intervals ranging from one minute to twelve minutes. For a given time interval, the ratio of the customized capnography tubing PCO<sub>2</sub> to the actual PCO<sub>2</sub> was quite constant (all standard errors < 0.02). For increasing time intervals, the ratio of the customized capnography tubing PCO<sub>2</sub> to the actual PCO<sub>2</sub> increased in a logarithmic fashion. The regression

coefficients were 0.89, and 0.85 for the 8 French customized capnography tubing in 5 and 10% CO<sub>2</sub> and 0.99 and 0.91 for the 6 French customized capnography tubing in the 5 and 10% CO<sub>2</sub>.

*Conclusions:* The described system was consistent and accurate in this in vitro system. It may be able to provide automated bedside gastrointestinal CO<sub>2</sub> partial pressure monitoring at very short intervals (e.g. 5 minutes), facilitating testing of the role of gastrointestinal P<sub>i</sub>CO<sub>2</sub> information in patient treatment algorithms.

**KEY WORDS:** tonometry; perfusion; acidosis; ischemia; mucosa; gut; shock; monitoring; carbon dioxide; critical illness

## INTRODUCTION

The gastrointestinal intraluminal partial pressure of carbon dioxide (P<sub>i</sub>CO<sub>2</sub>) reflects gastrointestinal mucosal cellular energy status and therefore the adequacy of mucosal perfusion irrespective of microvascular flow and mucosal PO<sub>2</sub>. (1-5) Gastrointestinal P<sub>i</sub>CO<sub>2</sub> increases as mucosal adenosine triphosphate (ATP) is depleted, remains elevated while perfusion remains inadequate, and should decrease when therapy restores an appropriate cellular ATP hydrolysis to ATP oxidative phosphorylation resynthesis ratio. (1-9) Inadequate gastrointestinal mucosal perfusion - indicated by an increasing P<sub>i</sub>CO<sub>2</sub> - occurs very early in shock, (1,2,6-17) sometimes persists during resuscitation, (12,14,18-26) and is

strongly associated with the later occurrence of organ dysfunctions and death.(21-38) In addition, the inclusion of gastrointestinal  $P_iCO_2$  information into trauma patient treatment algorithms appears to be beneficial.(24,25)

The current commercially available system for assessing gastrointestinal mucosal perfusion adequacy in patients consists of a silicone balloon at the end of a 16 French nasogastric or 7 French sigmoid catheter (TRIP NGS Catheter, Tonometrics, Inc., Hopkinton, MA). After tube placement, the silicone balloon is filled with saline, the  $PCO_2$  of which begins to equilibrate with the intraluminal  $PCO_2$ . After a measured equilibration interval of at least 20 minutes, the saline is withdrawn for  $PCO_2$  analysis using a blood gas analyzer. This methodology for measuring gastrointestinal  $P_iCO_2$  has several drawbacks: 1) a 20 minute or longer equilibration time, 2) significant  $CO_2$  partial pressure changes with solution temperature changes, 3) differences in measurement with different blood gas analyzers, and 4) multiple saline sample analyses by a blood gas analyzer as part of monitoring.(22,39-43) The use of succinylated gelatin 4% or phosphate buffered solution has been shown to help decrease the variance in  $PCO_2$  measurements among different blood gas analyzers;(42,43) however, the lag time, temperature concerns, procedural inconveniences, and costs per saline sample analysis remain unaffected.(22,39,40)

Infrared based  $P_iCO_2$  monitoring, on the other hand, has



the potential to avoid all of the previously mentioned drawbacks of saline tonometry. (22,39,40) Therefore, we developed a method for monitoring gastrointestinal  $P_iCO_2$  using existing end-tidal  $CO_2$  monitors and modified feeding tubes. We hypothesized that our customized capnography tubes would allow consistent tracking of  $PCO_2$  with an end-tidal infrared  $CO_2$  monitor. We tested our hypothesis by using our system to measure the  $PCO_2$  of a test chamber held at different known  $CO_2$  partial pressures.

#### **MATERIALS AND METHODS**

Customized capnography tubes (Figure 1) -  $CO_2$  permeable silicone tubing (1.47 mm ID, 1.96 mm OD, 12 cm or 6 cm length) was spliced into the distal ends of 8 or 6 French feeding tubes. Teflon tubing (0.31 mm ID, 0.78 mm OD) was inserted within the lumen of the feeding tube such that it ran along the entire length of the customized capnography tube. A 1.5 cm section of a 3.5 French umbilical catheter (Argyle, Sherwood Medical, St. Louis, MO) was used to attach the proximal end of the Teflon tubing to a blunted 20 gauge needle. The needle hub was connected to the sensing chamber of a mainstream end-tidal  $CO_2$  monitor (Novametrix Model 7100, Novametrix Medical Systems Inc., Wallingford, CT). The lengths of the customized capnography tubes' components are listed in Table 1.

Testing chamber - A 1.5 cm internal diameter tube was constantly flushed with a known concentration of  $\text{CO}_2$  (either 5% or 10%). The balance of each gas mixture was nitrogen ( $\text{N}_2$ ).

Testing technique (Figure 1) - Air samples were drawn through the customized capnography tubes and the infrared  $\text{CO}_2$  sensor chamber using an aquarium air pump with its two valves reversed as a negative pressure source (Penn-Plax Silent-Air·X2, Penn-Plax Inc., Garden City, NY). Infrared  $\text{CO}_2$  measurements of air taken directly from the test chamber provided the control values for the measurements obtained via the customized capnography tubes. Readings from the customized capnography tubes were obtained at discrete intervals. Ten readings per time interval were obtained at each of the one, two, three, four, and five minute intervals. Five readings per time interval were obtained at each of the six, eight, ten, and twelve minute intervals. The addition of a three-way solenoid valve and solenoid valve timer between the  $\text{CO}_2$  sensor and the modified air pump allowed for automation of this system. Readings were taken at five minute intervals with the solenoid valve and timer.

Statistical analysis - Equilibration curves were obtained for each of the customized capnography tubes by plotting the  $\text{PCO}_2$  obtained via the customized capnography tube (sample  $\text{PCO}_2$ ) divided by the control value (actual  $\text{PCO}_2$ ). Trendline equations and regression coefficients were calculated for each

customized capnography tube using a Microsoft Excel software package (Microsoft, Bothell, WA).

## RESULTS

The 5% CO<sub>2</sub>, 95% N<sub>2</sub> gas mixture had a directly measured PCO<sub>2</sub> of  $41 \pm .1$  torr (5.4 kPa) (n = 35). The 10% CO<sub>2</sub>, 90% N<sub>2</sub> gas mixture had a directly measured PCO<sub>2</sub> of  $80 \pm .1$  torr (10.5 kPa) (n = 46). The trendline equations and regression coefficients for each customized capnography tube in the 5% and 10% CO<sub>2</sub> gas mixtures are listed in Table 2. The equilibration plots for the 8 and 6 French customized capnography tubes are shown in Figures 2 and 3, respectively. For a given customized capnography tube and time interval, the ratio of the sample PCO<sub>2</sub> to the actual PCO<sub>2</sub> was quite constant. For increasing time intervals, the ratio of the customized capnography tube PCO<sub>2</sub> to the actual PCO<sub>2</sub> increased in a logarithmic fashion (Figures 2 and 3 and Table 2).

## DISCUSSION

Patients with inadequate gastrointestinal mucosal perfusion, indicated by an elevated gastrointestinal P<sub>i</sub>CO<sub>2</sub> (or decreased pH<sub>i</sub>) are at high risk for multiple organ dysfunction syndrome and death.(21-38) Monitoring for and timely correction of mucosal perfusion inadequacy appears to have potential for improving patient outcomes.(24,25,38,44) Therefore, GI P<sub>i</sub>CO<sub>2</sub> monitoring methods that avoid the

previously discussed drawbacks of saline tonometry may prove useful.

We describe a simple approach for automated monitoring of GI  $P_i\text{CO}_2$ . Because of the described system's consistency, any suitable customized capnography tubing combination can be easily calibrated (that is, a sample reading taken after a given time interval will be a known fraction of the actual  $\text{PCO}_2$ ). The important aspects of the customized capnography tubing are a feeding tube diameter and length paired with a  $\text{CO}_2$  permeable tubing length that result in an end-tidal infrared monitor waveform lasting from three to six seconds. This air flow resistance and mixing imposed restraint is the reason a 12 cm length of  $\text{CO}_2$  permeable tubing was used in the customized capnography tube of a suitable length for adult nasogastric placement. For the shorter, 6 French customized capnography tube, 6 cm of  $\text{CO}_2$  permeable tubing provided sufficient sample volume to obtain good readings. Smaller than 6 French diameter tubing (5 French) was found unsuitable (unpublished data). In addition to the tubing combinations, the use of a consistent constant negative pressure source for drawing the sample through the infrared  $\text{PCO}_2$  detection chamber is also important for system accuracy.

The use of only two gas mixtures with  $\text{CO}_2$  partial pressures above zero is a potential shortcoming of this study; however, the  $\text{CO}_2$  partial pressures of the two mixtures are representative of  $\text{CO}_2$  partial pressures indicating adequate

(41 mm Hg) and grossly inadequate (80 mm Hg) mucosal perfusion (assuming a normal arterial  $PCO_2$ ). The consistency of our data at both partial pressures, as shown by the small standard errors, reflects the ability of this system to track  $PCO_2$  with a high degree of precision ( $r^2 \geq 0.9$ ).

Our GI  $P_iCO_2$  monitoring approach offers several advantages over saline tonometry. Our approach allows unlimited automated GI  $P_iCO_2$  monitoring at much shorter time intervals than can be used with saline tonometry while avoiding the problems associated with saline samples.(22,39-43) Although automation of our system does involve a one time equipment cost of approximately \$220, sample collection charges and saline sample analysis charges are avoided (\$8.20 and \$35.90, respectively, per sample at our institution). Each customized capnography tube costs approximately \$4.61 to \$5.67 as compared to a saline gastric tonometer which is currently priced between \$100 to \$150. Our approach does require an end-tidal infrared capnometer, but this allows for bedside GI  $P_iCO_2$  monitoring while removing the need for a blood gas analyzer and avoiding the aforementioned problems with saline samples.

In summary, we report here the results of our in vitro testing of a simple system designed to provide frequent measurements of GI  $P_iCO_2$ . Further studies with this system will determine its usefulness in vivo. Only with the provision of timely and accurate GI  $P_iCO_2$  data will we be able

to adequately test the role of GI  $P_iCO_2$  information in patient treatment algorithms.

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**FIGURE LEGENDS**

Figure 1. Schematic of a customized capnography tube and the PCO<sub>2</sub> monitoring system.

Figure 2. Equilibration plot for the 8 French customized capnography tube. All standard errors less than 0.02.

Figure 3. Equilibration plot for the 6 French customized capnography tube. All standard errors less than 0.008.

**TABLES**

Table 1. Tubing lengths involved in making each customized capnography tube. The teflon tubing length is the same as the total length of the customized capnography tube.

Customized capnography tube diameter	Feeding tube length	Feeding tube diameter	Teflon tubing length	Silicone tubing length
8 French	97.9 cm	8 French	113.8 cm	12 cm
6 French	51.6 cm	6 French	59.9 cm	6 cm

Table 2. Trendline equations and regression coefficients for different customized capnography tubes.

Customized capnography tube	% CO <sub>2</sub>	Equation	Regression coefficient
8 French	5%	$y=0.0822\ln(x)+0.547$	$R^2=0.8929$
8 French	10%	$y=0.0892\ln(x)+0.5212$	$R^2=0.8512$
6 French	5%	$y=0.0573\ln(x)+0.4126$	$R^2=0.9904$
6 French	10%	$y=0.0717\ln(x)+0.3744$	$R^2=0.9134$

### customized capnography tube

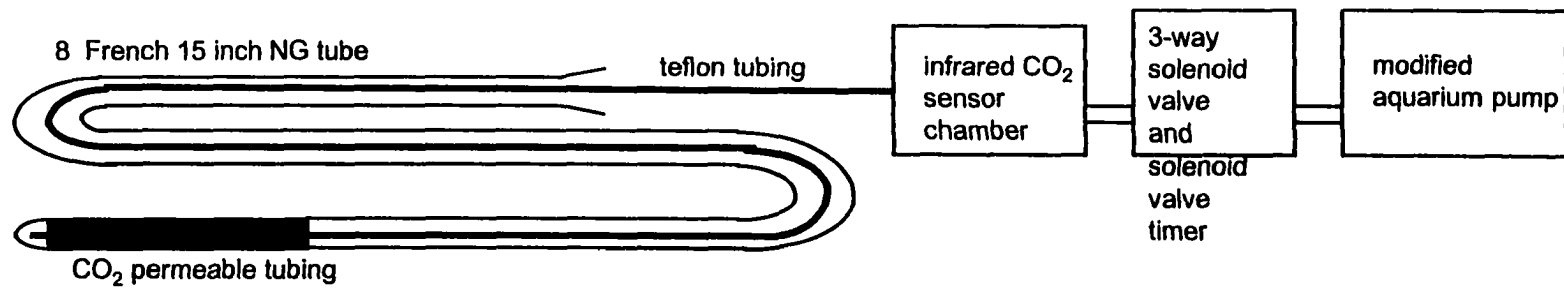


Figure 1

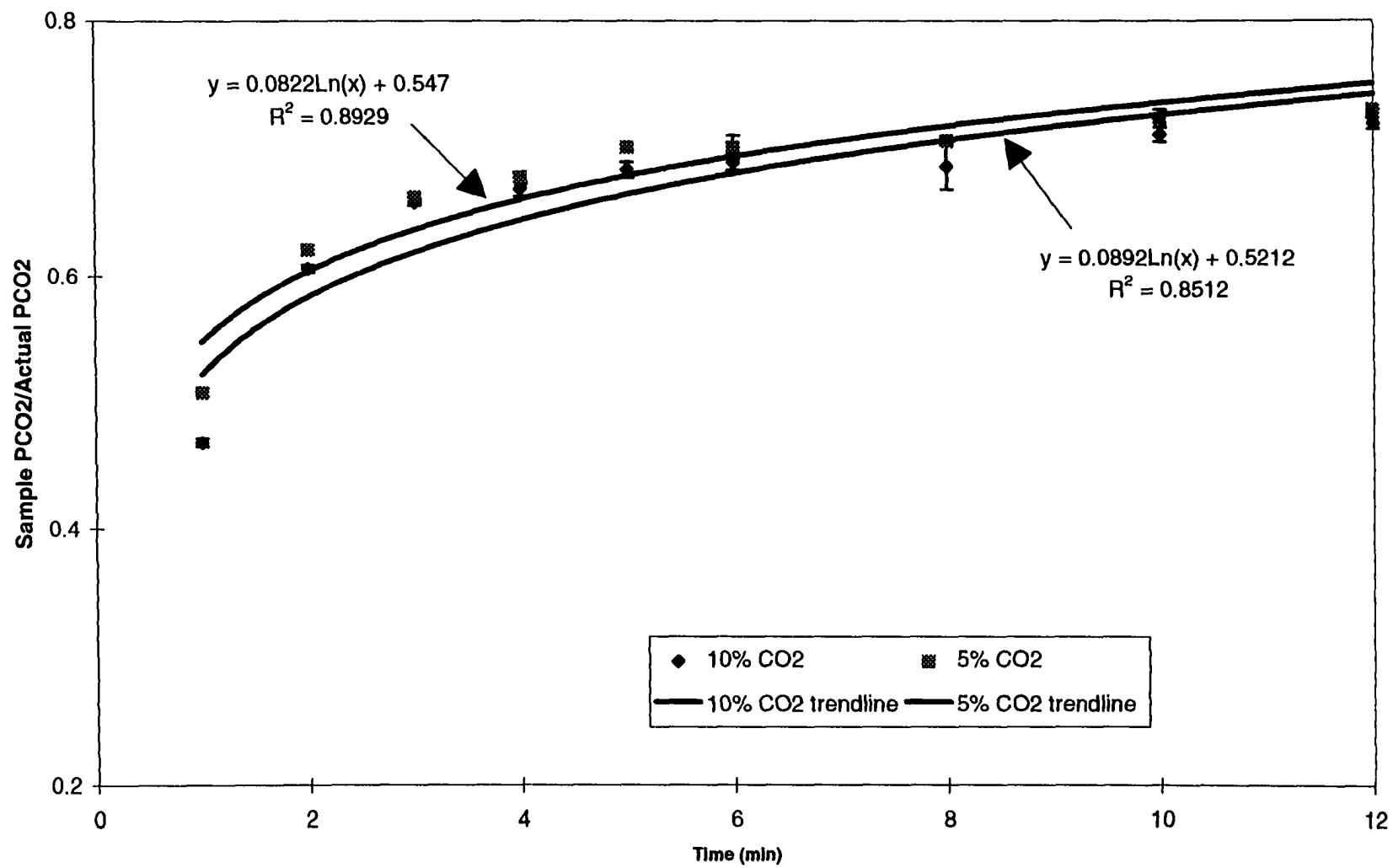


Figure 2

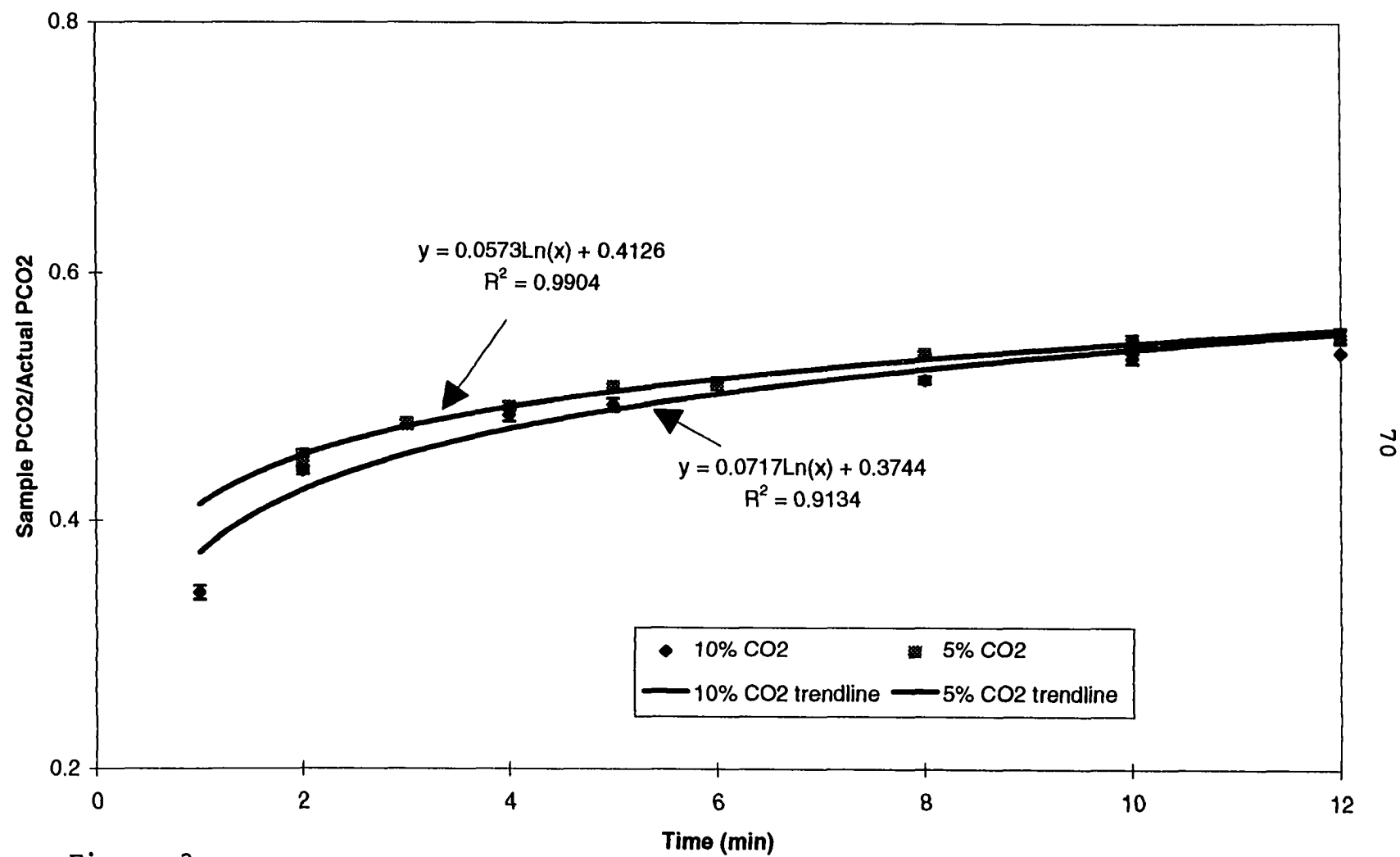


Figure 3



COLONIC  $P_iCO_2$  AND OUTCOME DURING HEMORRHAGIC SHOCK AND  
RESUSCITATION IN RATS

A paper that will be submitted to J Surg Res

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**Abstract**

*Objective:* To examine the relationship between colonic intraluminal  $CO_2$  partial pressure ( $P_iCO_2$ ) and outcome in a rat model of hemorrhage and resuscitation.

*Design:* Randomized, controlled animal study.

*Materials and Methods:*  $CO_2$  permeable silicone tubing connected via nonpermeable tubing to a syringe pump on one end and an infrared  $CO_2$  monitor on the other was placed transrectally into the colon of 23 non-fasted, non-heparinized Wistar-Furth rats for colonic  $P_iCO_2$  monitoring during two hours of hemorrhage such that mean arterial pressure stayed between 35 and 40 mm Hg and three hours of intravenous fluid maintaining the mean arterial pressure  $\geq$  75 mm Hg. Rats that survived 48 hours were euthanized.

*Measurements and Main Results:* The rat mortality in this model was 35%. The rats that died before 48 hours (non-survivors) had higher colonic  $P_iCO_2$ s than the 48 hour survivors

(beginning of hemorrhage: non-survivors,  $69 \pm 3$  mm Hg; survivors,  $59 \pm 3$  mm Hg; five minutes into resuscitation: non-survivors,  $90 \pm 7$  mm Hg; survivors,  $66 \pm 3$  mm Hg; 120 minutes into resuscitation: non-survivors,  $59 \pm 3$  mm Hg; survivors,  $52 \pm 1$  mm Hg). Despite the severity of the model (60% incidence of renal tubular necrosis, 48% incidence of small intestinal necrosis, and 10% incidence of hepatic necrosis), no pulmonary pathology characteristic of the acute respiratory distress syndrome was observed.

*Conclusions:* The presence of an elevated  $P_iCO_2$  in some rats before the start of hemorrhage suggests that the stress responses of these rats to anesthesia and the minor surgery involved in catheter placement were sufficient to cause some mucosal ATP synthesis inadequacy. While an elevated colonic  $P_iCO_2$  was predictive for rat mortality, the severe hemorrhagic shock attained in this model did not provide a sufficient inflammatory insult to cause pathologic changes characteristic of the acute respiratory distress syndrome.

*Key Words:* Hemorrhage, trauma, shock, resuscitation, gastrointestinal mucosa, carbon dioxide, monitoring, outcome assessment, gastrointestinal tonometry

## Introduction

Trauma is the leading cause of death in the first four decades of life in the United States,<sup>1</sup> and multiple organ dysfunction syndrome (MODS) is the cause of most late (> 48

hours of hospitalization) trauma deaths.<sup>2</sup> Hemorrhagic shock is intimately linked with trauma. Decreases in gastrointestinal perfusion occur early in hemorrhage<sup>3,4</sup> and lead to elevations in gastrointestinal intraluminal CO<sub>2</sub> partial pressure (P<sub>i</sub>CO<sub>2</sub>).<sup>5-10</sup> Hemorrhagic shock induced elevations in P<sub>i</sub>CO<sub>2</sub> often persist despite resuscitative efforts.<sup>11-15</sup> Persistent elevations in gastrointestinal P<sub>i</sub>CO<sub>2</sub> (or decreases in gastrointestinal pH<sub>i</sub>, calculated using P<sub>i</sub>CO<sub>2</sub>) are strongly associated with the development of multiple organ dysfunction syndrome (MODS) and death in trauma<sup>11-15</sup> and surgical<sup>16-20</sup> patients. Additionally, timely correction of gastrointestinal P<sub>i</sub>CO<sub>2</sub>, generally having been achieved by systemic cardiovascular interventions believed to increase mucosal perfusion, appears to have potential for improving trauma patient outcomes.<sup>11,14</sup> Since rat models are commonly used to investigate both hemorrhagic shock and the mechanisms involved in the development of multiple organ dysfunction syndrome, we hypothesized that colonic P<sub>i</sub>CO<sub>2</sub> in hemorrhaged and resuscitated rats would be associated with outcome (death and organ pathology) in a manner similar to that reported in human trauma patients. A positive finding would support the use of this model for examining the mechanisms linking an elevated P<sub>i</sub>CO<sub>2</sub> to adverse outcomes and for evaluating possible therapeutic interventions.

## Materials and Methods

This study was conducted with the approval of the Animal Care and Use Committee, Veterans' Administration Medical Center, Des Moines, Iowa. All experiments were undertaken in the Des Moines Veterans' Administration Medical Center's AAALAC accredited Surgery Laboratory in accordance with the provisions of the USDA Animal Welfare Act, the PHS Guide for the Care and Use of Laboratory Animals, and the U.S. Interagency Research Animal Committee Principles for the Utilization and Care of Research Animals.

Animal Model. Since Sprague-Dawley rats are allergic to dextran-containing solutions,<sup>21,22</sup> Wistar-Furth rats, which are not allergic to dextran,<sup>22</sup> were used for all experiments.

Animal Instrumentation. Nonfasted male Wistar-Furth rats, weighing  $309.8 \pm 4.6$  g (range: 267.9 - 372.1 g), were anesthetized with ketamine (50 mg/kg intramuscularly) and pentobarbital (40 mg/kg subcutaneously). The skin incision sites (the ventral cervical midline and the left groin) were prepared by clipping the fur, swabbing the skin with alcohol followed by betadine, and injecting 1% lidocaine along the planned location of the incision. The tubing (Figure 1) for measuring  $P_iCO_2$  was then advanced through the rectum into the colon. Number 3 French heparin-bonded polyurethane catheters (Cook, Inc.) were then surgically placed into the femoral artery for bleeding, the left external jugular vein for delivering fluids, and the left carotid artery for monitoring

blood pressure.

GI  $P_i\text{CO}_2$ . The GI  $P_i\text{CO}_2$  monitoring system, patterned after a design published by Larsen, Pedersen, and Moesgaard,<sup>13</sup> involved placing highly  $\text{CO}_2$  permeable tubing (12 cm length, 0.2 ml volume, 1.47 mm ID, 1.96 mm OD silicone) into the GI tract (Figure 1).  $\text{CO}_2$  produced in the colon diffused into the lumen of the  $\text{CO}_2$  permeable tubing and was delivered in air through  $\text{CO}_2$  impermeable tubing to an infrared mainstream end-tidal  $\text{CO}_2$  monitor (Novametrics) for quantification. To minimize lag time, non- $\text{CO}_2$ -containing dilutional air flowing at 0.198 ml/minute was added to the post-permeable tubing  $\text{CO}_2$  equilibrated air, which passed through the  $\text{CO}_2$  permeable tubing at a flow rate of 0.066 ml/minute. With the mixed air (three parts non- $\text{CO}_2$  dilutional air/one part  $\text{CO}_2$  equilibrated air) flowing at 0.264 ml/minute, lag time was reasonably short. *In vitro* testing of this  $\text{PCO}_2$  monitoring system was performed by placing the  $\text{CO}_2$  permeable tubing in an inverted one liter glass bottle immersed in a  $37^\circ\text{C}$  water bath and flushed continuously with 95%  $\text{N}_2$  and 5%  $\text{CO}_2$  (directly measured  $\text{PCO}_2$  of 40 mm Hg). The results were quite reproducible; the mean  $\text{PCO}_2 \pm 1 \text{ SEM}$  was  $36.9 \pm .4$  mm Hg for 25 readings (92.2% of the directly measured  $\text{PCO}_2$ ).

Hemorrhagic Shock and Resuscitation. We used a non-heparinized, pressure-controlled hemorrhagic shock model in which the animal's own compensatory responses to blood loss controlled the volume of the hemorrhage, the duration of the

hemorrhage, and the volume of resuscitation fluid used. Thirty minutes after instrumentation and positioning in sternal recumbency, rats were allowed to bleed through the femoral artery catheter as necessary to reach and maintain a mean arterial blood pressure between 35 and 40 mm Hg. Intravenous fluid resuscitation commenced after two hours of hemorrhage or if mean arterial pressure fell below 30 mm Hg for ten minutes or 25 mm Hg for one minute. The goal of intravenous fluid resuscitation was to reach and maintain a mean arterial pressure above 75 mm Hg for three hours using one of the following three fluids: (a) lactated Ringer's infused at 1 ml/min ( $n = 8$ ), (b) 6% dextran 70 mixed with lactated Ringer's solution infused at 1 ml/min ( $n = 9$ ), or (c) 7.8% NaCl in 6% dextran 70 infused at 1 ml/min and 6% dextran 70 mixed with lactated Ringer's infused at 1 ml/min (total flow with both solutions, 2 ml/min) ( $n = 6$ ). The 6% dextran 70 mixed with lactated Ringer's solution was designed to replace interstitial fluid (3/7 lactated Ringer's) and intravascular volume (4/7 6% dextran 70). In the experiments in which 7.8% NaCl in 6% dextran 70 was used, the maximum volume of 7.8% NaCl administered was 4 ml/kg. If additional fluid was needed to maintain blood pressure, the 6% dextran 70 mixed with lactated Ringer's was continued at 1 ml/min.

Assessments. *Cardiorespiratory status.* Mean arterial pressure was monitored continuously throughout the procedures. Arterial hematocrit, total plasma protein,  $PO_2$  ( $P_{aO_2}$ ),  $PCO_2$

( $P_aCO_2$ ), arterial pH ( $pH_a$ ), and arterial base excess were measured at the start of hemorrhage, at five minutes into resuscitation, and at 120 minutes into resuscitation. A blood sample was taken five minutes into resuscitation instead of at the start of resuscitation because the rats were unable to tolerate withdrawal of the one-half ml of blood required for blood-gas analysis at end-hemorrhage. Total blood lost, volume of fluid returned, and body weight changes were also assessed. *GI mucosal perfusion adequacy.* Colonic  $P_iCO_2$  was measured at 20-minute intervals throughout the procedures. *Histological analysis.* Tissue samples from the liver, kidney, lungs, and small intestine were taken at the time of death (non-survivors) or after euthanasia at 48 hours and prepared in standard fashion for histological examination. Necrosis and neutrophil infiltration were rated on a 0 to 4 point scale<sup>24</sup> by a pathologist who was unaware of the sample's treatment group (0 indicated normal tissue and 4 indicated extensive, severe necrosis and infiltration).

Statistical Analyses. Significance of differences between mean values for continuous variables were assessed with two-way analysis of variance statistics (ANOVA) for repeated measures and Fisher's protected LSD *post hoc* testing. Categorical data were evaluated for significance using the Fisher's exact test. Means  $\pm$  1 SEM are reported.

Power Analysis. Using the assumption that the resuscitation fluid would have a large effect (corresponding

to a difference of 0.80 standard deviation units) on the dependent variable ( $P_iCO_2$  or organ damage) and setting the probability level ( $\alpha$ ) at 0.05, 20 animals were planned per resuscitation fluid group; however, the lack of acute respiratory distress type pulmonary pathology in any of the 23 rats reported on in this paper led to a change in our experimental protocol.

## Results

Of the 23 hemorrhaged rats, two rats resuscitated with 7.8% NaCl in 6% dextran 70 died five and 20 minutes into resuscitation, respectively. Two lactated Ringer's rats, three 6% dextran 70 mixed with lactated Ringer's rats, and one additional 7.8% NaCl in 6% dextran 70 rat died between two and 36 hours after intravenous fluid resuscitation ended. Only six lactated Ringer's rats, six 6% dextran 70 mixed with lactated Ringer's rats, and three 7.8% NaCl in 6% dextran 70 rats survived to 48 hours.

One of each of these was allowed a longer survival period (three days, seven days, and seven days respectively) to evaluate any late developing organ damage. None was found.

Also, one of the lactated Ringer's 48 hour survival rats was excluded from any comparisons beyond five minutes of resuscitation because the fluid pump was mistakenly left on for 52 minutes despite a mean arterial pressure greater than 75 mm Hg during this time.



Variables for which no significant differences were found between the survivors and the non-survivors both within their respective fluid resuscitation groups and independent of their fluid resuscitation groups are as follows: duration of hemorrhage (survivors,  $97 \pm 6$  minutes; non-survivors,  $93 \pm 5$  minutes); extent of hemorrhage (survivors,  $24.1 \pm 0.7$  ml/kg; non-survivors,  $26.8 \pm 1.5$ ); hematocrit and total plasma protein at the start of hemorrhage, five minutes into resuscitation, and 120 minutes into resuscitation; and  $P_aO_2$  and  $P_aCO_2$  at the start of hemorrhage, five minutes into resuscitation, and 120 minutes into resuscitation. The volume of resuscitation fluid administered varied according to the type of fluid used (lactated Ringer's,  $80.4 \pm 17.4$  ml/kg; 6% dextran 70 mixed with lactated Ringer's,  $25.7 \pm 7.6$  ml/kg; 7.8% NaCl in 6% dextran 70 followed by 6% dextran 70 mixed with lactated Ringer's  $22.3 \pm 6.6$  ml/kg). The change in body weight from before anesthesia to the end fluid resuscitation reflected the volume of fluid administered (lactated Ringer's,  $4.6 \pm 2.1\%$  of body weight gained; 6% dextran 70 mixed with lactated Ringer's,  $2.1 \pm 0.6\%$  of body weight lost; 7.8% NaCl in 6% dextran 70  $3.3 \pm 0.3\%$  of body weight lost). The arterial pH ( $pH_a$ ) of the survivors was different from that of the non-survivors at the start of hemorrhage (survivors,  $7.374 \pm 0.010$ ; non-survivors,  $7.409 \pm 0.012$ ;  $p = 0.04$ ) and five minutes into resuscitation (survivors,  $7.190 \pm 0.017$ ; non-survivors,  $7.081 \pm 0.036$ ;  $p = 0.005$ ) but not 120 minutes into

resuscitation (survivors,  $7.434 \pm 0.017$ ; non-survivors,  $7.380 \pm 0.033$ ;  $p = 0.1$ ).

The base excess became more negative during hemorrhage ( $p < 0.01$ ) and less negative during resuscitation ( $p < 0.01$ ). (See Figure 2.) Survivors had less negative base excesses than non-survivors ( $F(1,21) = 9.78$ ,  $p < 0.005$ ). A base excess more negative than -15 five minutes into resuscitation was 71% sensitive and 87% specific for mortality before 48 hours.

The colonic  $P_iCO_2$  increased during hemorrhage ( $p < 0.01$ ) and decreased during resuscitation ( $p < 0.05$ ) (See Figure 3.) Evidence of GI vascular insufficiency was grossly visible (purple to black small or large bowel) at necropsy in four of the eight rats that had colon  $P_iCO_2s \geq 82$  mm Hg. Of the eight rats with colon  $P_iCO_2s \geq 82$  mm Hg, only two survived to 48 hours; both had colon  $P_iCO_2s$  of 85 mm Hg at the start of resuscitation, and neither had gross or histologic evidence of bowel infarction at necropsy. No rats with colon  $P_iCO_2s < 82$  mm Hg had evidence of a bowel infarction. Survivors had lower  $P_iCO_2s$  than non-survivors ( $F(1,21) = 16.08$ ,  $p < 0.0006$ ). A colon  $P_iCO_2$  of  $\geq 82$  mm Hg at the start of resuscitation was 75% sensitive and 87% specific for mortality.

Mortality in this model was 35%. No histological evidence of neutrophil infiltration was found in any examined tissue of either those rats that died before 48 hours or those rats that survived to euthanasia. Figures 4a and b show the incidence and severity of bronchopneumonia, hepatic necrosis,

renal tubular necrosis, and small intestinal necrosis in those rats that died before 48 hours and in those that survived to euthanasia. The greater severity of hepatic, renal, and small intestinal necrosis observed in the rats that died versus those that survived did not reach statistical significance.

## Discussion

Hemorrhagic shock leads to elevations in gastrointestinal  $P_i\text{CO}_2$  by decreasing mucosal perfusion adequacy such that mitochondrial resynthesis of ATP is insufficient to balance ATP hydrolysis ( $\text{ATP} \rightarrow \text{ADP} + P_i + \text{H}^+$ ;  $\text{H}^+ + \text{HCO}_3^- \rightarrow \text{H}_2\text{CO}_3 \rightarrow \text{CO}_2 + \text{H}_2\text{O}$  as supported by the work of Schlichtig and Bowles<sup>7</sup> and described in reviews by Fiddian-Green<sup>8</sup> and Gutierrez<sup>9</sup>). Increases in GI  $P_i\text{CO}_2$  (or calculated decreases in GI  $\text{pH}_i$ ) occur very early in humans during cardiovascular compromise<sup>6</sup> and, especially when persistent,<sup>11-14,16,20,25-27</sup> are strongly associated with MODS<sup>11-19,28</sup> and death<sup>11-16,18-20,26-30</sup> in patients. Additionally, timely correction of GI mucosal energy status, generally having been achieved by systemic cardiovascular interventions believed to increase mucosal perfusion, appears to have potential for improving patient outcomes.<sup>11,14,29</sup> These clinical data support a contributing role for depletion of the energy stores in cells in the mucosal layer of the GI tract for driving the development of MODS in patients.

A general scheme to explain how energy depletion in cells in the mucosal layer of the GI tract contributes to MODS

development follows: 1) cardiovascular compromise, 2) decrease in splanchnic perfusion<sup>3,4,31-34</sup> (at least partly mediated by angiotensin II<sup>35-37</sup>), 3) inadequate GI mucosal oxygenation to support matching of ATP hydrolysis by ATP resynthesis via oxidative phosphorylation (results in increasing GI  $P_iCO_2$ <sup>7-10</sup>) and inadequate oxygen partial pressure to support respiratory burst killing of bacteria by either enterocytes<sup>38</sup> or resident phagocytes (mucosal  $PO_2$  of 4 mm Hg has been reported for a rat hemorrhage and resuscitation model<sup>39</sup>), 4) increase in GI permeability<sup>40-42</sup> and increase in bacterial and toxin translocation,<sup>41,43-46</sup> 5) generation of proinflammatory cytokines<sup>44-47</sup> by enterocytes<sup>48</sup> and gut associated lymphoid tissue,<sup>44,47</sup> 6) priming<sup>49-52</sup> and increases in adhesiveness<sup>49,50</sup> of neutrophils (xanthine oxidase generation of  $O_2^-$  may be involved<sup>53</sup> as may platelet activating factor<sup>49-52,54</sup>), 7) promotion of and contribution to the systemic inflammatory response by proinflammatory cytokines<sup>44,55,56</sup> and primed<sup>53,54</sup> and sticky<sup>57,58</sup> neutrophils,<sup>40</sup> 8) failure of systemic resuscitative measures to restore adequate GI mucosal ATP resynthesis by oxidative phosphorylation<sup>59,5,11-15</sup> continues to promote systemic inflammatory response,<sup>18</sup> and 9) development and progression of inflammatory organ damage and dysfunction (multiple organ dysfunction syndrome).

To test the mechanisms linking inadequate gastrointestinal mucosal mitochondrial ATP resynthesis to the development and progression of multiple organ dysfunction

syndrome, a model that shows a relationship between gastrointestinal  $P_iCO_2$  and outcome similar to that reported in patients would be helpful. Therefore, we determined whether such an association existed in this hemorrhage and resuscitation model. As shown in Figure 3, non-survivors had significantly higher colonic  $P_iCO_2$ s five minutes into resuscitation and 120 minutes into resuscitation than did rats that survived to 48 hours. This observation supports the hypothesis that rat gastrointestinal  $P_iCO_2$  is related to mortality in a manner similar to that reported in trauma and surgery patients. Interestingly, colonic  $P_iCO_2$  indicated that some rats, especially in the group that did not survive to 48 hours ( $p < 0.05$ ), already had inadequate mucosal perfusion to meet mucosal demands. This coincides with the findings of Mythen and Web<sup>17</sup> that not all presurgical patients have optimal wedge pressures without fluid administration and that failure to optimize cardiovascular status during the perioperative period is associated with a greater incidence of mucosal hypoperfusion (56% vs 7%,  $p < 0.001$ ) which is associated with a greater incidence of post-surgical complications (6 vs 0,  $p = 0.01$ ).

In addition to the association between  $P_iCO_2$  and mortality, we found a significant association between a more negative base excess and mortality (Figure 2). A similar association between an admission base excess and poor outcome has been reported in trauma patients.<sup>59-63</sup> This finding was

expected and further supports the relevance of this model for investigating clinical questions.

Considerable organ pathology (survivors and non-survivors combined; 10% incidence of hepatic necrosis, 60% incidence of renal tubular necrosis, 48% incidence of small intestinal damage) was observed. While the incidence of bronchopneumonia appeared to be greater in the survivors and the severity of liver, kidney, and small intestinal pathology appeared to be greater in non-survivors, none of the incidence or severity differences depicted in Figures 4a and 4b reached significance.

Despite the model severity (35% mortality and the above mentioned incidence of organ pathology), pulmonary pathology characteristic of the acute respiratory distress syndrome was not observed. This is an important difference from what is reported in trauma patients in that development of the acute respiratory distress syndrome is typical for those patients who develop multiple organ dysfunction syndrome within 72 hours.<sup>63</sup> Since trauma patients by definition suffer from mechanical tissue damage as well as blood loss prior to developing the acute respiratory distress syndrome and other organ dysfunction, it was not unlikely that an additional insult beyond hemorrhagic shock might be required in rats as well (possibly something as simple as positive pressure ventilation<sup>64</sup>). The absence of inflammatory pulmonary pathology in this model led to modification of this model

before 20 animals were done in each resuscitation group.

Animal models which have  $P_iCO_2$  associations with outcome similar to those reported in patients are important for determination of the mechanisms which link an elevated  $P_iCO_2$  to poor outcomes (e.g. neutrophil priming from increased gastrointestinal permeability). Animal models should also help determine which interventions are best for decreasing an elevated  $P_iCO_2$  and for suggesting the possible impact on patient outcomes of treatment algorithms incorporating such interventions in response to an elevated  $P_iCO_2$ . While this model showed a strong association between an elevated  $P_iCO_2$  and mortality, the absence of inflammatory pulmonary pathology characteristic of that seen in multiple organ dysfunction syndrome<sup>65</sup> suggests that this model should be modified. A simple modification that would be expected to enhance the adverse effects of hemorrhagic shock on the gut mucosa would be the addition of a pre-hemorrhage fast. The finding of inflammatory pulmonary pathology with such a modification would support the importance of gastrointestinal mucosal status as an important contributor to distant organ pathology.

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### Legends

Figure 1. GI  $P_iCO_2$  monitoring system.

Figure 2. a. Base excess in rats that died before 48 hours versus those that survived to 48 hours. b. The averages for the survivors at five minutes and 120 minutes into resuscitation are significantly higher than the averages for the non-survivors ( $*p < 0.01$ ). Solid lines with solid triangles ( $\blacktriangle$ ) represent the survivors; dotted lines with solid circles ( $\bullet$ ) represent the non-survivors. Abbreviations: 5 min R, five minutes into resuscitation; 120 min R, 120 minutes into resuscitation.

Figure 3. a. Colonic  $P_iCO_2$  in rats that died before 48 hours versus those that survived to 48 hours. b. The averages for the survivors at the start of hemorrhage and 5 minutes into resuscitation are significantly lower than the averages for the non-survivors ( $*p < 0.05$  at start hemorrhage,  $**p < 0.01$  at 5 min R). Solid lines with solid triangles ( $\blacktriangle$ ) represent the survivors; dotted lines with solid circles ( $\bullet$ ) represent the non-survivors. Abbreviations: 5 min R, five minutes into resuscitation; 120 min R, 120 minutes into resuscitation. The error bar for the 120 min R time point for the rats that survived to 48 hours is within the symbol.

Figure 4. a. Incidence of histopathology in rats that died before 48 hours versus those that survived to 48 hours. b. Severity of histopathology on a 0 to 4 point scale of increasing severity in rats that died before 48 hours versus those that survived to 48 hours. Neither lung inflammation characteristic of the acute respiratory distress syndrome nor lung edema was observed. Of the 8 rats that died, histopathology was obtained on only 6. Histopathology was obtained on all 15 that survived. Abbreviations: broncho, bronchopneumonia; inflam, inflammation; sm int, small intestine.

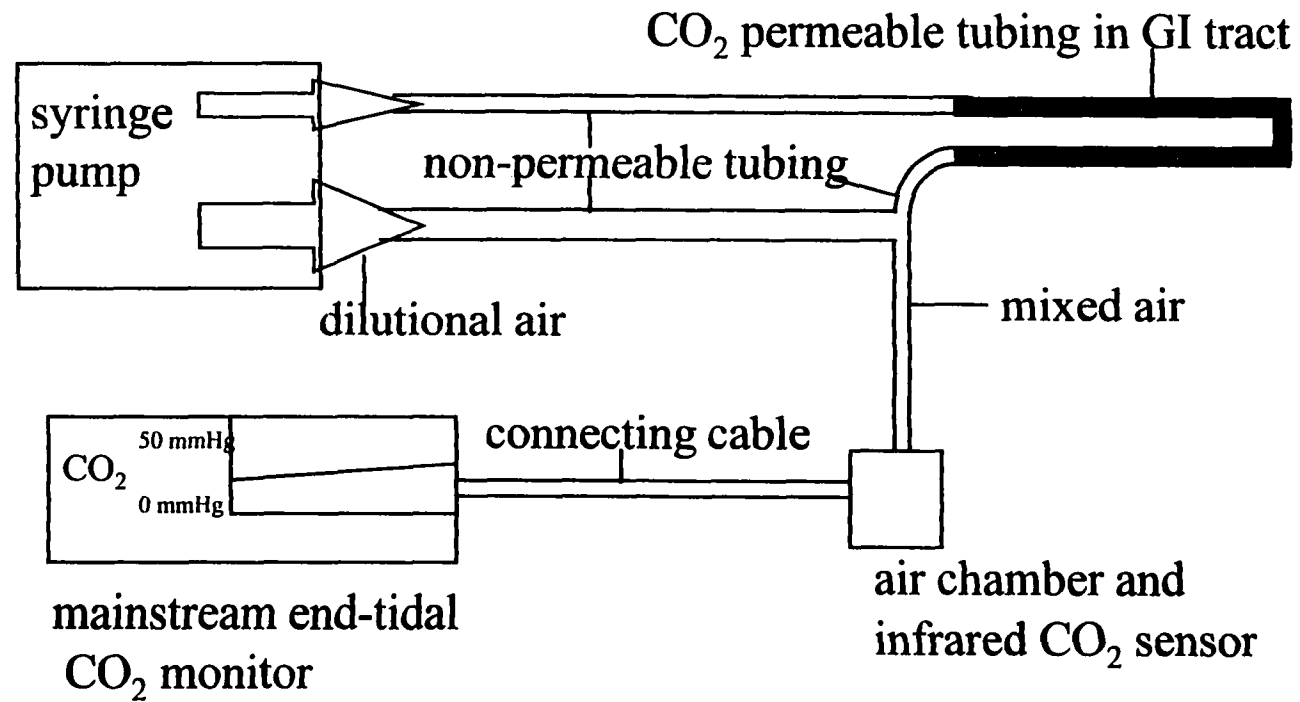
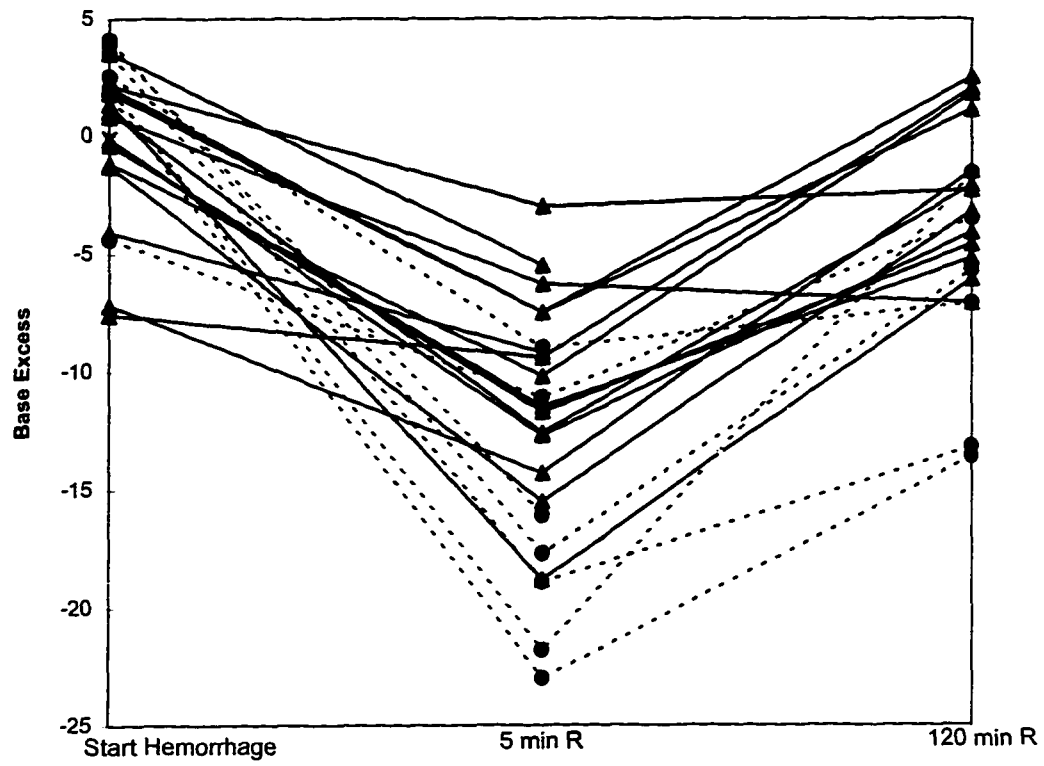
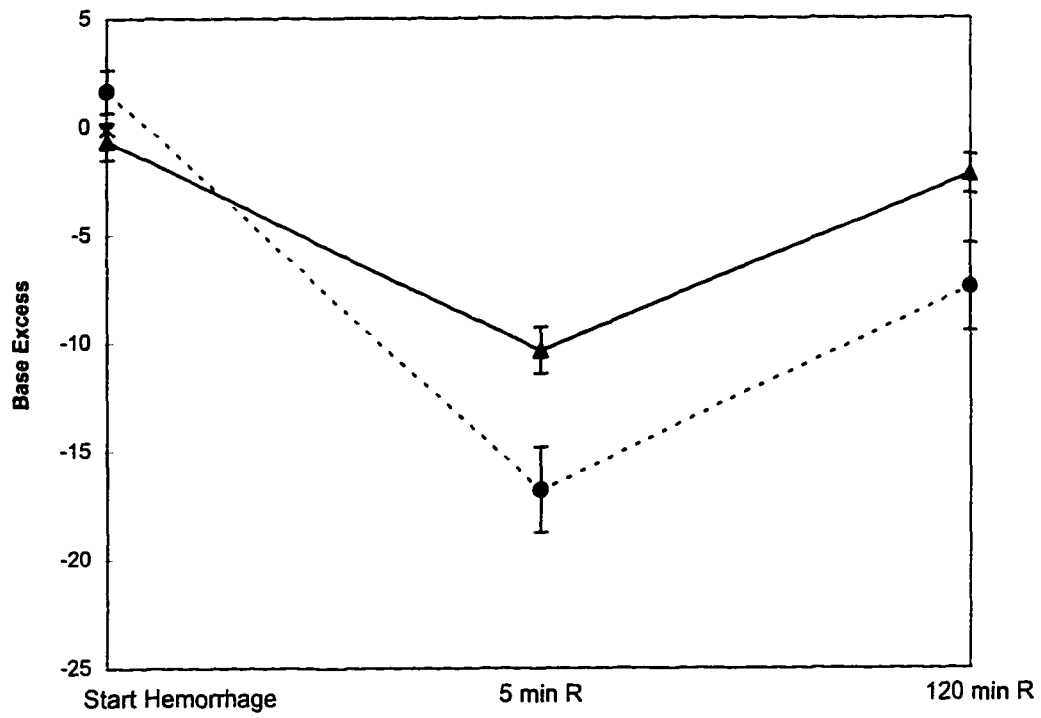


Figure 1

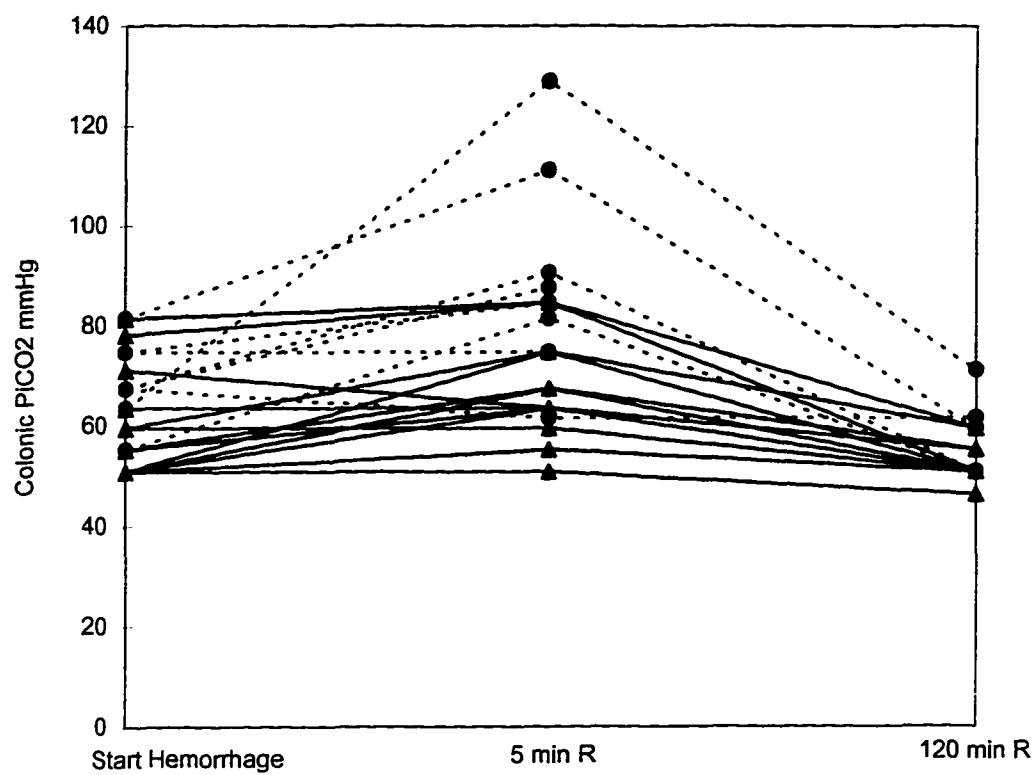


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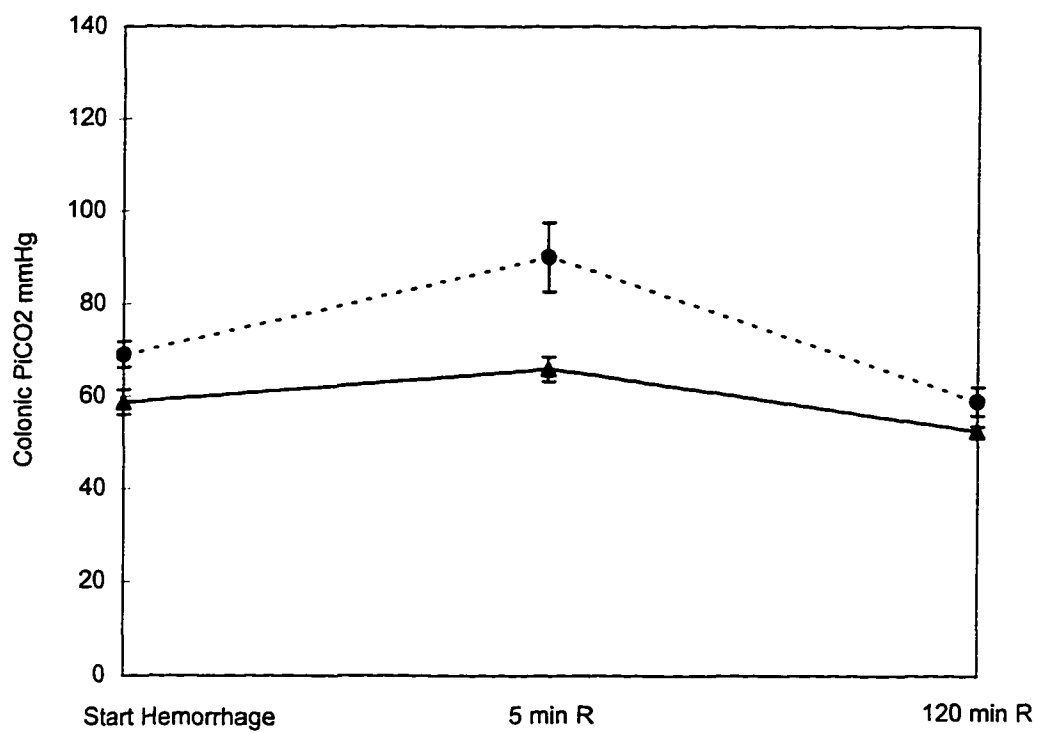


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Figure 2



a

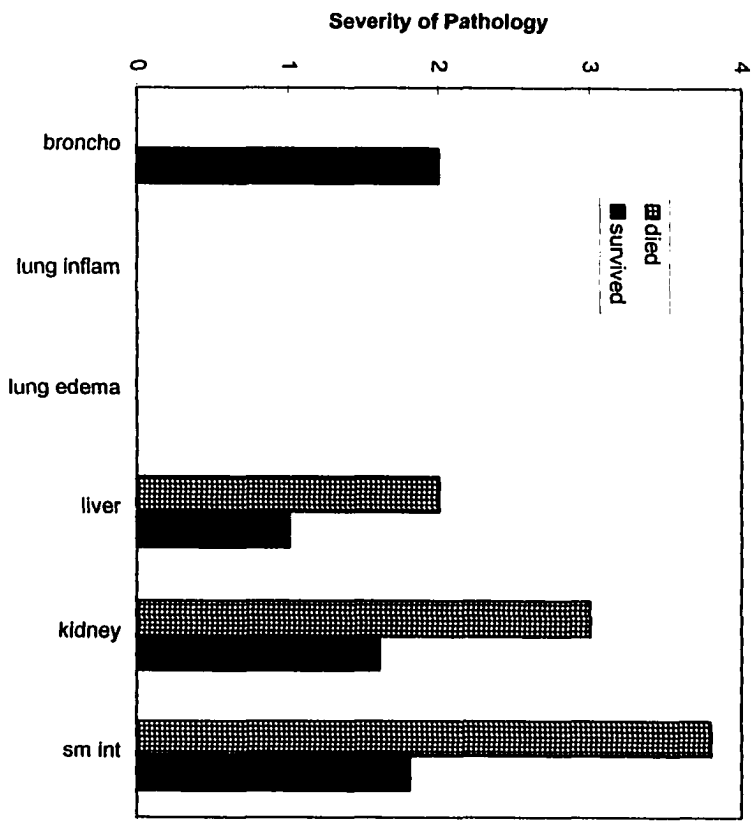


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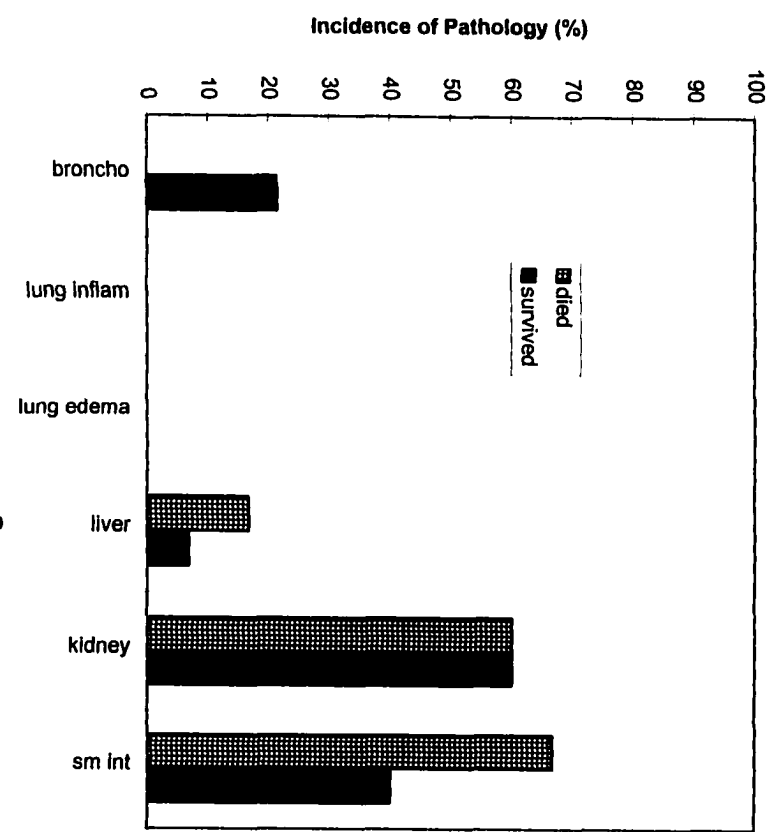
Figure 3

Figure 4

b



a



PRE-HEMORRHAGE FASTING AFFECTS OUTCOME AND THE PREDICTIVE  
POWER OF COLONOC  $P_iCO_2$  IN RATS

A paper that will be submitted to J Surg Res

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**Abstract**

*Objective:* To examine the effect of pre-hemorrhage  
fasting on colonic intraluminal  $CO_2$  partial pressure ( $P_iCO_2$ )  
and outcome in a rat model of hemorrhage and resuscitation.

*Design:* Randomized, controlled animal study.

*Materials and Methods:* With (F, n = 74) or without (NF, n  
= 23) an 18 hour pre-hemorrhage fast, non-heparinized male  
Wistar-Furth rats were allowed to hemorrhage for two hours  
(mean arterial pressure 35 - 40 mm Hg) followed by intravenous  
fluid resuscitation for three hours (1ml/min as needed to  
maintain mean arterial pressure  $\geq$  75 mm Hg). Rats that  
survived 48 hours were euthanized.

*Measurements and Main Results:* With a pre-hemorrhage  
fast, the start of resuscitation colonic  $P_iCO_2$  and base excess  
did not differentiate between survivors and non-survivors (NF  
survivors  $66 \pm 3$  mm Hg and  $-10.4 \pm 1.1$ ; NF non-survivors  $90 \pm$   
 $7$  mm Hg,  $p < 0.05$  and  $-16.8 \pm 2.0$ ,  $p < 0.05$ ; F survivors  $62 \pm 2$  mm



Hg and  $-13.6 \pm 0.5$ ; F non-survivors  $59 \pm 2$  mm Hg and  $-14.4 \pm 0.6$ ). Fasting increased the incidence of organ pathology and mortality (pulmonary inflammation and edema: NF 0%, F 26%,  $p < 0.05$ ; hepatic necrosis: NF 10%, F 45%,  $p < 0.05$ ; renal necrosis: NF 60%, F 47%; small intestinal necrosis: NF 48%, F 85%,  $p < 0.05$ ; mortality: NF 35%, F 66%,  $p < 0.05$ ).

**Conclusions:** Pre-hemorrhage fasting significantly affects outcome and the predictive power of  $P_iCO_2$  and base excess. How fasting decreases the predictive power of these measurements for mortality in this model and whether pre-surgery fasting decreases the value of patient  $P_iCO_2$  monitoring and increases patient risk should be determined.

**Key Words:** Hemorrhage, trauma, shock, resuscitation, gastrointestinal mucosa, carbon dioxide, monitoring, outcome assessment, gastrointestinal tonometry

## Introduction

Trauma is the leading cause of death in the first four decades of life in the United States,<sup>1</sup> and multiple organ dysfunction syndrome (MODS) is the cause of most late (> 48 hours of hospitalization) trauma deaths.<sup>2</sup> Hemorrhagic shock is intimately linked with trauma. Decreases in gastrointestinal perfusion occur early in hemorrhage<sup>3,4</sup> and lead to elevations in gastrointestinal intraluminal  $CO_2$  partial pressure ( $P_iCO_2$ ).<sup>5-10</sup> Hemorrhagic shock induced elevations in  $P_iCO_2$  often persist despite resuscitative

efforts.<sup>11-15</sup> Persistent elevations in gastrointestinal  $P_iCO_2$  (or decreases in gastrointestinal  $pH_i$ , calculated using  $P_iCO_2$ ) are strongly associated with the development of multiple organ dysfunction syndrome (MODS) and death in trauma<sup>11-15</sup> and surgical<sup>16-20</sup> patients. Additionally, timely correction of gastrointestinal  $P_iCO_2$ , generally having been achieved by systemic cardiovascular interventions believed to increase mucosal perfusion, appears to have potential for improving trauma patient outcomes.<sup>11,14</sup> Elevations in  $P_iCO_2$  similar to those reported in patients were associated with mortality in our non-fasted rat model of hemorrhagic shock and resuscitation (submitted for publication). Since no pulmonary pathology consistent with the acute respiratory distress syndrome was noted in that model, we hypothesized that fasting before hemorrhage, an additional gastrointestinal mucosa stressor, would result in pulmonary pathology characteristic of the acute respiratory distress syndrome and increased mortality. We also hypothesized that different resuscitation protocols would be associated with differences in  $P_iCO_2$  and, therefore, differences in outcome.

## **Materials and Methods**

This study was conducted with the approval of the Animal Care and Use Committee, Veterans' Administration Medical Center, Des Moines, Iowa. All experiments were undertaken in the Des Moines Veterans' Administration Medical Center's

AAALAC accredited Surgery Laboratory in accordance with the provisions of the USDA Animal Welfare Act, the PHS Guide for the Care and Use of Laboratory Animals, and the U.S. Interagency Research Animal Committee Principles for the Utilization and Care of Research Animals.

Animal Model. Since Sprague-Dawley rats are allergic to dextran-containing solutions,<sup>21,22</sup> Wistar-Furth rats, which are not allergic to dextran,<sup>22</sup> were used for all experiments.

Animal Instrumentation. After an 18 hour fast with water available, male Wistar-Furth rats, weighing  $257.3 \pm 3.3$  g (range: 212.1 - 316.8 g), were anesthetized with ketamine (25 mg/kg intramuscularly) and pentobarbital (25 mg/kg subcutaneously). The skin incision sites (the ventral cervical midline and the left groin) were prepared by clipping the fur, swabbing the skin with alcohol followed by betadine, and injecting 1% lidocaine along the planned location of the incision. The silicone portion of the customized capnography tubing (Figure 1) for measuring  $P_i\text{CO}_2$  was then advanced through the rectum into the colon. Number 3 French heparin-bonded polyurethane catheters (Cook, Inc.) were then surgically placed into the femoral artery for bleeding, the left external jugular vein for delivering fluids, and the left carotid artery for monitoring blood pressure.

Customized Capnography Tubing. (Figure 1.)  $\text{CO}_2$  permeable silicone tubing (1.47 mm ID, 1.96 mm OD, 6 cm length) was spliced into the distal end of an 8 French, 15

inch feeding tube. Teflon tubing (0.31 mm ID, 0.78 mm OD) was inserted within the lumen of the feeding tube such that it ran along the entire length of the feeding tube and the silicone tubing.

P<sub>i</sub>CO<sub>2</sub> Measurement. A 1.5 cm section of a 3.5 French umbilical catheter (Argyle, Sherwood Medical, St. Louis, MO) was used to attach the proximal end of the teflon tubing to a blunted 20 gauge needle. The needle hub was connected to the sensing chamber of a mainstream end tidal CO<sub>2</sub> monitor (Novamatrix Model 7100, Novamatrix Medical Systems Inc., Wallingford, CT). Air samples were drawn through the customized capnography tubes and the infrared CO<sub>2</sub> sensor chamber using an aquarium air pump with its two valves reversed as a negative pressure source (Penn-Plax Silent-Air-X2, Penn-Plax Inc., Garden City, NY). A three-way solenoid valve and solenoid valve timer between the CO<sub>2</sub> sensor and the modified air pump allowed for automation of this system. *In vitro* testing of this PCO<sub>2</sub> monitoring system was carried out in 95% N<sub>2</sub> and 5% CO<sub>2</sub> and 90% N<sub>2</sub> and 10% CO<sub>2</sub>. The readings from air samples drawn every 5 minutes represent 54 ± 1% of the actual PCO<sub>2</sub>.

Hemorrhagic Shock. We used a non-heparinized, pressure-controlled hemorrhagic shock model in which the animal's own compensatory responses to blood loss controlled the volume of the hemorrhage, the duration of the hemorrhage, and the volume of resuscitation fluid used. Thirty minutes after

instrumentation and positioning in sternal recumbency, rats were allowed to bleed through the femoral artery catheter as necessary to reach and maintain a mean arterial blood pressure between 35 and 40 mm Hg. Intravenous fluid resuscitation commenced after two hours of hemorrhage or if mean arterial pressure fell below 30 mm Hg for ten minutes or 25 mm Hg for one minute.

Resuscitation. The goal of intravenous fluid resuscitation was to reach and maintain a mean arterial pressure above 75 mm Hg for three hours. An additional goal in one half of the rats in each fluid group was to reach and maintain a  $P_i\text{CO}_2 \leq 50$  mm Hg by administering one to two boluses of enalaprilat (0.06 mg/kg). Enalaprilat was only administered if the mean arterial pressure was greater than 75 mm Hg, the  $P_i\text{CO}_2$  was greater than 50 mm Hg, and, in the case of a second dose of enalaprilat, more than 30 minutes had elapsed since the first dose. The intravenously administered resuscitation fluids were as follows: (a) lactated Ringer's infused at 1 ml/min ( $n = 26$ , 12 without enalaprilat and 14 with enalaprilat), (b) 6% dextran 70 mixed with lactated Ringer's solution infused at 1 ml/min ( $n = 26$ , 14 without enalaprilat and 12 with enalaprilat), or (c) 7.8% NaCl in 6% dextran 70 infused at 1 ml/min followed by 6% dextran 70 mixed with lactated Ringer's also infused at 1 ml/min ( $n = 13$ ). The 6% dextran 70 mixed with lactated Ringer's solution was designed to replace interstitial fluid (3/7 lactated Ringer's)

and intravascular volume (4/7 6% dextran 70). In the experiments in which 7.8% NaCl in 6% dextran 70 was used, the maximum volume of 7.8% NaCl administered was to be 4 ml/kg. Any additional fluid for maintenance of blood pressure would have been the 6% dextran 70 mixed with lactated Ringer's. Each rat was randomly assigned to a resuscitation protocol at the start of anesthesia.

Assessments. *Cardiorespiratory status.* Mean arterial pressure was monitored continuously throughout the procedures. Arterial hematocrit, total plasma protein,  $PO_2$  ( $P_aO_2$ ),  $PCO_2$  ( $P_aCO_2$ ), arterial pH ( $pH_a$ ), and arterial base excess were measured at the start of hemorrhage, at five minutes into resuscitation, and at 120 minutes into resuscitation. A blood sample was taken five minutes into resuscitation instead of at the start of resuscitation because the rats were unable to tolerate withdrawal of the one-half ml of blood required for blood-gas analysis at end-hemorrhage. In rats that died before five minutes of resuscitation, a blood sample taken just after death was run for base excess. Total blood lost and volume of fluid returned were also assessed. *GI mucosal perfusion adequacy.* Colonic  $P_iCO_2$  was measured at 5-minute intervals throughout the procedures. *Histological analysis.* Tissue samples from the liver, kidney, lungs, and small intestine were taken at the time of death (non-survivors) or after euthanasia at 48 hours and prepared in standard fashion for histological examination. Necrosis and neutrophil

infiltration were rated on a 0 to 4 point scale<sup>23</sup> by a pathologist who was unaware of the sample's treatment group.

Statistical Analyses. Significance of differences between mean values for continuous variables were assessed with analysis of variance statistics (ANOVA) for repeated measures and Fisher's protected LSD *post hoc* testing. Categorical data were evaluated for significance using the Fisher's exact test. Means  $\pm$  1 SEM are reported.

Power Analysis. Using the assumption that the resuscitation protocol would have a large effect (corresponding to a difference of 0.80 standard deviation units) on the dependent variable ( $P_iCO_2$  or organ damage) and setting the probability level ( $\alpha$ ) at 0.05, 20 animals were planned per resuscitation protocol group; however, the loss of predictive power for mortality of the start of resuscitation  $P_iCO_2$  reported in this paper led to an interruption of this study. The limited number of rats receiving the hypertonic saline dextran reflects the 100% mortality at the start of resuscitation observed in that group.

## Results

Of the 74 hemorrhaged rats, nine died during hemorrhage, before the start of any resuscitation. The 13 that received the hypertonic saline dextran died at the start of resuscitation and are discussed as a separate group elsewhere (submitted for publication). Three rats in the 6% dextran 70

mixed with lactated Ringer's group, including one rat that would have been able to receive enalaprilat, died early in resuscitation (30 seconds, 10 minutes, and 1 minute into resuscitation). Two rats in the lactated Ringer's group, both of which would have been able to receive enalaprilat, died early in resuscitation (1 minute each).

The duration and extent of hemorrhage were  $85 \pm 3$  minutes and  $23.1 \pm 0.6$  ml/kg, respectively. The hematocrit, total plasma protein,  $P_aO_2$ ,  $P_aCO_2$ , and  $pH_a$  were not different between survivors and non-survivors and among resuscitation protocols. Among the rats that survived more than three hours, the volume of resuscitation fluid administered varied according to the type of fluid and was not affected by the administration of enalaprilat (lactated Ringer's,  $95.1 \pm 11.8$  ml/kg; 6% dextran 70 mixed with lactated Ringer's,  $23.2 \pm 3.3$  ml/kg).

The base excess became more negative during hemorrhage ( $p < 0.01$ ) and less negative during resuscitation ( $p < 0.01$ ) (Figure 2), and the colonic  $P_iCO_2$  increased during hemorrhage ( $p < 0.01$ ) and decreased during resuscitation ( $p < 0.01$ ) (Figure 3). In contrast to the results in non-fasted rats, however, survivors and non-survivors could not be distinguished by either base excess or  $P_iCO_2$ . Exclusion of all rats that died before three hours of resuscitation had no effect on the base excess' or the  $P_iCO_2$ 's lack of discrimination between rats that did not survive for 48 hours.

Mortality in this model was 66%. Figures 4a and b show



the incidence and severity of bronchopneumonia, pulmonary inflammation and edema, hepatic necrosis, renal tubular necrosis, and small intestinal necrosis in those rats that died before 48 hours and in those that survived to euthanasia.

## Discussion

The results obtained in these rats fasted prior to hemorrhage are quite different from what we observed in rats that were not fasted before hemorrhage. The incidence of pulmonary inflammation and edema (non-fasted, 0%; fasted, 26%;  $p < 0.05$ ,  $\chi^2$ ), hepatic necrosis (non-fasted, 10%; fasted, 45%;  $p < 0.05$ ,  $\chi^2$ ), small intestinal necrosis (non-fasted, 48%; fasted, 85%;  $p < 0.05$ ,  $\chi^2$ ) and mortality (non-fasted, 35%; fasted, 66%;  $p < 0.05$ ,  $\chi^2$ ) all increased. It is more likely that the above differences resulted from the pre-hemorrhage fast than from the decrease in pentobarbital<sup>24</sup> (non-fasted, 40 mg/kg; fasted 25 mg/kg) or the difference in the  $P_iCO_2$  monitoring tubing system. These data suggest an important role for enteral nutrients in protecting the gut and, thereby, distant organs during or after the stress of hemorrhagic shock. The absence of luminal energy substrates might become critically important to mucosal cells when their cardiovascular supply of  $O_2$  and nutrients is diminished. Additionally, in the absence of luminal nutrients, less blood flows to the gastrointestinal tract,<sup>25,26</sup> mucosal immunity decreases,<sup>27</sup> and bacterial adherence increases.<sup>28</sup> The linking

mechanisms between pre-hemorrhage fasting and increased pulmonary inflammation might involve some degree of neutrophil priming and adhesion molecule upregulation during fasting or greater neutrophil priming and adhesion molecule upregulation during hemorrhage because of a more compromised gut barrier.

While pre-hemorrhage fasting increased organ damage and mortality, it also eliminated the power of both base excess and colon  $P_iCO_2$  at the start of resuscitation to predict which rats would and would not survive to 48 hours. In fact, the average  $P_iCO_2$  in the non-survivors after 120 minutes of resuscitation was actually slightly lower than the average  $P_iCO_2$  in the survivors ( $p < 0.01$ ). This is contrary to what has been reported in trauma patients<sup>11-15</sup> (who are not generally fasted before trauma) and surgery patients<sup>16-20</sup> (who are commonly fasted six to eight hours or more before surgery). If  $P_iCO_2$  is truly reflective of ATP hydrolysis unmatched by mitochondrial ATP resynthesis, the results in our fasted rats might be explained in several ways: 1) fasting protected mucosal ATP levels; 2) fasting uncoupled the association between unbalanced mucosal ATP hydrolysis and adverse outcome; or 3) fasting decreased the starting mucosal cellular mass or individual cellular ATP content to such an extent that  $H^+$  production from ATP hydrolysis was markedly reduced and a higher  $P_iCO_2$  in this context represented a greater preservation of mucosal cells. <sup>31</sup>P nuclear magnetic resonance spectroscopy may allow the determination of how closely an increasing  $P_iCO_2$

that is not caused by an increasing  $P_a\text{CO}_2$  tracks a decreasing ATP to ADP ratio and which, if any, of the above three reasons accounted for the absence of a higher  $P_i\text{CO}_2$  in non-surviving fasted rats.

The differences in outcomes and  $P_i\text{CO}_2$ s as predictors of outcome observed in these rats raise some possible questions in regards to fasting patients before surgery. Does pre-surgery fasting of humans increase patient risk? If so, a pre-surgery fast of what duration is required to increase risk (linear relationship, increasing risk to a plateau, no increase in risk followed by a sharp rise in risk, increasing risk followed by decreasing risk, etc.)? Would consumption of a simple electrolyte and glucose solution be sufficient to decrease risk or would a more complex solution be required? And, how does pre-surgery fasting affect the value of monitoring gastrointestinal  $P_i\text{CO}_2$  in patients?

### Acknowledgements

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**Legends**

Figure 1. GI  $P_iCO_2$  monitoring system.

Figure 2. Base excess in rats that died before 48 hours versus those that survived to 48 hours. The average base excess for the survivors at two hours into resuscitation is significantly higher than the average for the non-survivors ( $p < 0.01$ ). Abbreviations: start H, start hemorrhage; start R, five minutes into resuscitation; 2 hr R, two hours into resuscitation.

Figure 3. Colonic  $P_iCO_2$  in rats that died before 48 hours versus those that survived to 48 hours. The average colonic  $P_iCO_2$  for the survivors at the two hours into resuscitation is significantly higher than the average for the non-survivors ( $p < 0.05$ ). Abbreviations: start H, start hemorrhage; start R, five minutes into resuscitation; 2 hr R, two hours into resuscitation.

Figure 4. a. Incidence of histopathology in rats that died before 48 hours versus those that survived to 48 hours. b. Severity of histopathology on a 0 to 4 point scale of increasing severity in rats that died before 48 hours versus those that survived to 48 hours. Abbreviations: broncho, bronchopneumonia; inflam, inflammation; sm int, small intestine.



### customized capnography tube

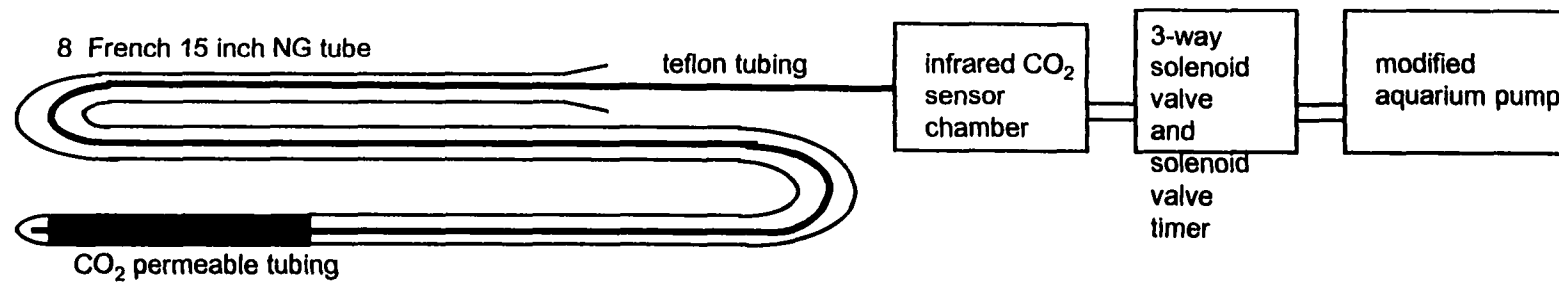


Figure 1

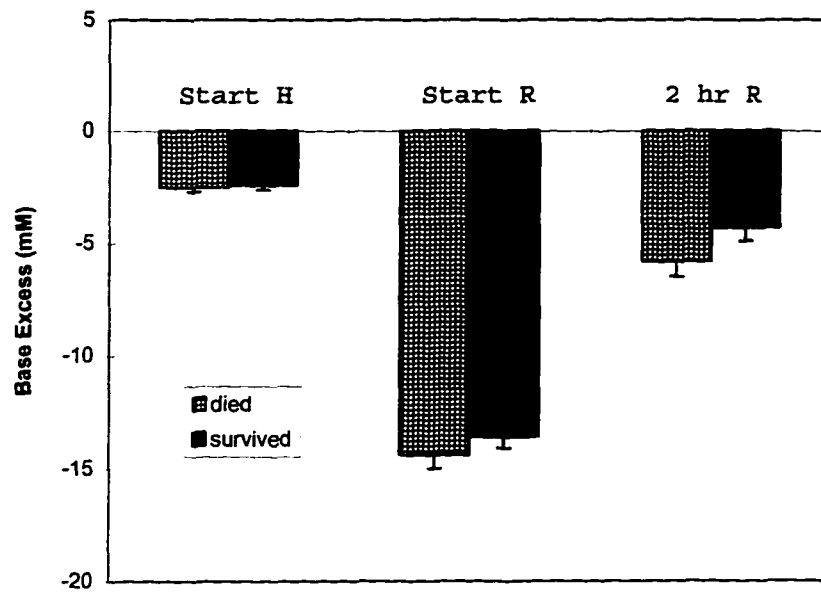


Figure 2

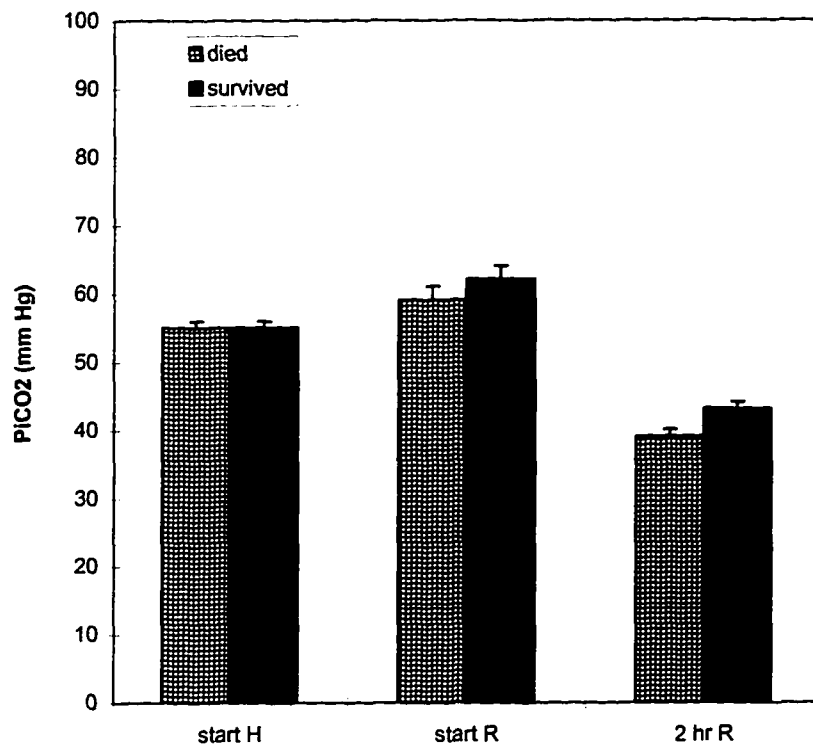
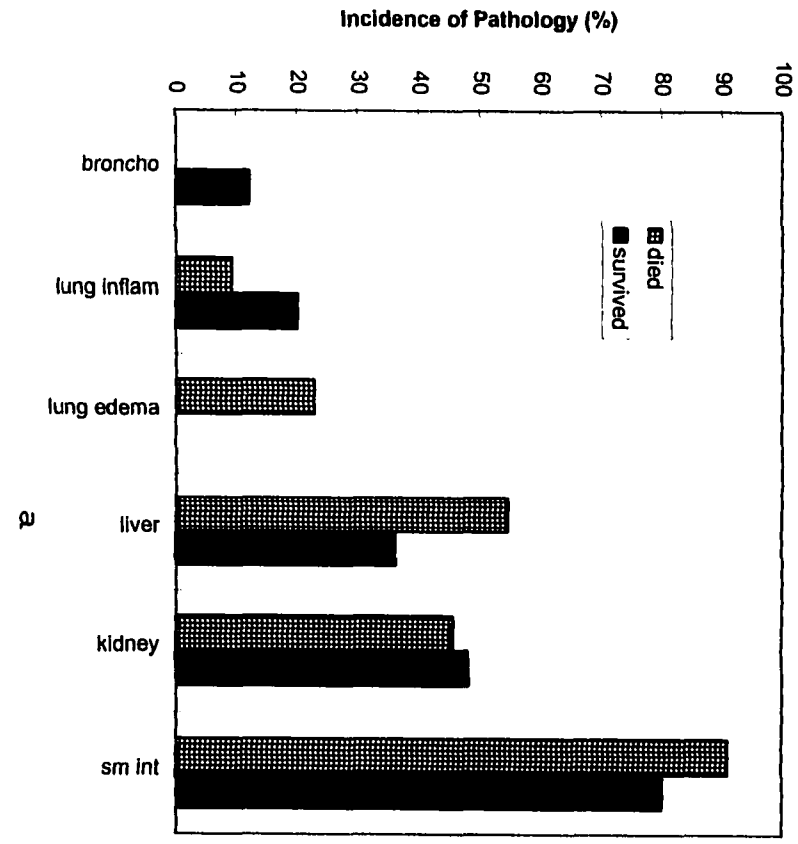
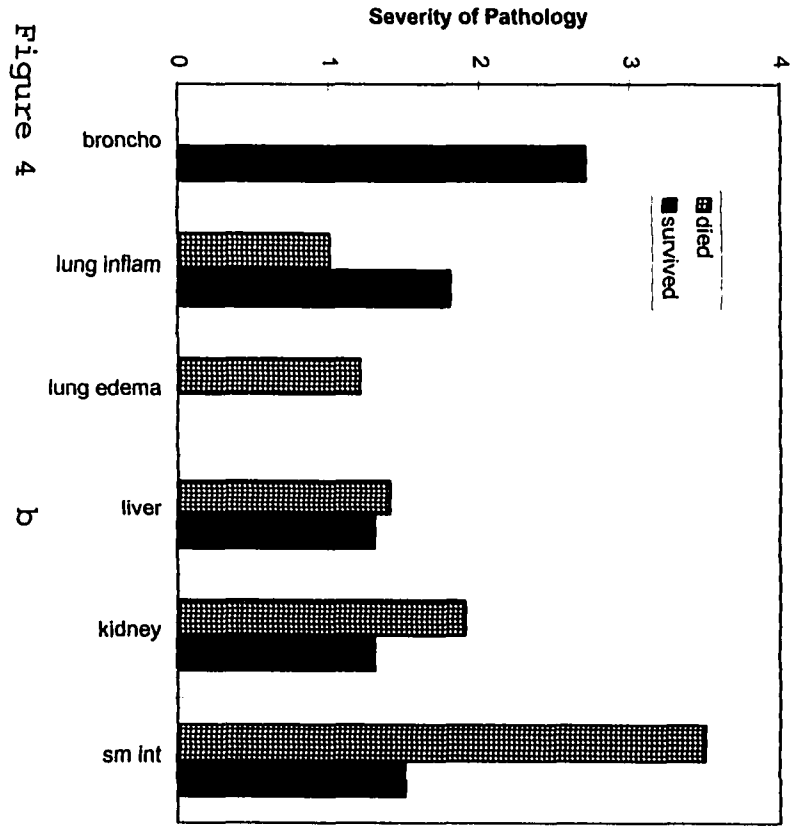


Figure 3

Figure 4



**RAPID ADMINISTRATION OF HYPERTONIC SALINE DEXTRAN CAN CAUSE  
RESPIRATORY COMPROMISE**

A paper that will be submitted to J Surg Res  
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**Abstract**

*Objective:* To compare the effect on outcome of resuscitation with hypertonic saline dextran versus 6% dextran 70 and lactated Ringer's in a rat model of hemorrhage and resuscitation.

*Design:* Retrospective analysis of a randomized, controlled animal study.

*Materials and Methods:* After an 18 hour pre-hemorrhage fast, 74 non-heparinized male Wistar-Furth rats were allowed to hemorrhage for two hours (mean arterial pressure 35 - 40 mm Hg) followed by intravenous fluid resuscitation for three hours with lactated Ringer's, 6% dextran 70 mixed with lactated Ringer's, or 7.8% NaCl in 6% dextran 70 (1 ml/min as needed to maintain mean arterial pressure  $\geq$  75 mm Hg). Rats that survived 48 hours were euthanized.

*Measurements and Main Results:* Nine rats died before the start of resuscitation. Each of the 13 rats that received

7.8% NaCl in 6% dextran 70 died  $39 \pm 2$  seconds into resuscitation. Only three of 26 rats that received 6% dextran 70 mixed with lactated Ringer's and two of 26 rats that received lactated Ringer's died during resuscitation.

*Conclusions:* Rapid administration (4 ml/kg in approximately 1.3 minutes in this study) of 7.8% NaCl in 6% dextran 70 to resuscitate from severe hemorrhagic shock is not safe. When using 7.8% NaCl in 6% dextran 70, respiration should be carefully monitored and the ability to mechanically ventilate should be assured.

*Key Words:* Hemorrhage, trauma, shock, resuscitation, hypertonic saline, monitoring, respiration

## **Introduction**

Hypertonic saline dextran solutions have been used for rapid resuscitation of hemorrhagic shock in both research models<sup>1-5</sup> and trauma patients.<sup>7-9</sup> In research models, resuscitation with hypertonic saline dextran solutions has been shown to more quickly restore cardiac output<sup>1-3</sup> and to improve microvascular perfusion to a greater extent than resuscitation with lactated Ringer's or normal saline.<sup>4,5</sup> Also in research models, rapid decreases in arterial pH ( $\text{pH}_a$ ), base excess, and respiratory rate have been reported with the bolus administration (4 ml/kg over 4 minutes in pigs<sup>1</sup> and 4 ml/kg over 1 to 2 minutes in sheep<sup>2</sup>) of hypertonic saline dextran solutions, but such decreases rapidly resolve.

This study is a retrospective analysis of the results obtained with hypertonic saline dextran in a prospective, randomized controlled animal study evaluating the effects of different resuscitation protocols on gastrointestinal intraluminal CO<sub>2</sub> partial pressure (P<sub>i</sub>CO<sub>2</sub>). In that study, we encountered apnea and 100% mortality in the rats which recieved hypertonic saline. Therefore, we propose that rapid hypertonic saline administration (4 ml/kg over approximately 1.3 minutes) for resuscitation from severe hemorrhagic shock may be unsafe due to respiratory compromise.

#### **Materials and Methods**

This study was conducted with the approval of the Animal Care and Use Committee, Veterans' Administration Medical Center, Des Moines, Iowa. All experiments were undertaken in the Des Moines Veterans' Administration Medical Center's AAALAC accredited Surgery Laboratory in accordance with the provisions of the USDA Animal Welfare Act, the PHS Guide for the Care and Use of Laboratory Animals, and the U.S. Interagency Research Animal Committee Principles for the Utilization and Care of Research Animals.

Animal Model. Since Sprague-Dawley rats are allergic to dextran-containing solutions,<sup>10,11</sup> Wistar-Furth rats, which are not allergic to dextran,<sup>11</sup> were used for all experiments.

Animal Instrumentation. After an 18 hour fast with water available, male Wistar-Furth rats, weighing  $257.3 \pm 3.3$  g

(range: 212.1 - 316.8 g), were anesthetized with ketamine (25 mg/kg intramuscularly) and pentobarbital (25 mg/kg subcutaneously). The skin incision sites (the ventral cervical midline and the left groin) were prepared by clipping the fur, swabbing the skin with alcohol followed by betadine, and injecting 1% lidocaine along the planned location of the incision. The silicone portion of the customized capnography tubing (Figure 1) for measuring  $P_i\text{CO}_2$  was then advanced through the rectum into the colon. Number 3 French heparin-bonded polyurethane catheters (Cook, Inc.) were then surgically placed into the femoral artery for bleeding, the left external jugular vein for delivering fluids, and the left carotid artery for monitoring blood pressure.

Customized Capnography Tubing. (Figure 1.)  $\text{CO}_2$  permeable silicone tubing (1.47 mm ID, 1.96 mm OD, 6 cm length) was spliced into the distal end of an 8 French, 15 inch feeding tube. Teflon tubing (0.31 mm ID, 0.78 mm OD) was inserted within the lumen of the feeding tube such that it ran along the entire length of the feeding tube and the silicone tubing.

$P_i\text{CO}_2$  Measurement. A 1.5 cm section of a 3.5 French umbilical catheter (Argyle, Sherwood Medical, St. Louis, MO) was used to attach the proximal end of the teflon tubing to a blunted 20 gauge needle. The needle hub was connected to the sensing chamber of a mainstream end tidal  $\text{CO}_2$  monitor (Novametrix Model 7100, Novametrix Medical Systems Inc.,

Wallingford, CT). Air samples were drawn through the customized capnography tubes and the infrared CO<sub>2</sub> sensor chamber using an aquarium air pump with its two valves reversed as a negative pressure source (Penn-Plax Silent-Air X2, Penn-Plax Inc., Garden City, NY). A three-way solenoid valve and solenoid valve timer between the CO<sub>2</sub> sensor and the modified air pump allowed for automation of this system. In vitro testing of this PCO<sub>2</sub> monitoring system was carried out in 95% N<sub>2</sub> and 5% CO<sub>2</sub> and 90% N<sub>2</sub> and 10% CO<sub>2</sub>. The readings from air samples drawn every 5 minutes represent  $54 \pm 1\%$  of the actual PCO<sub>2</sub>.

Hemorrhagic Shock. We used a non-heparinized, pressure-controlled hemorrhagic shock model in which the animal's own compensatory responses to blood loss controlled the volume of the hemorrhage, the duration of the hemorrhage, and the volume of resuscitation fluid used. Thirty minutes after instrumentation and positioning in sternal recumbency, rats were allowed to bleed through the femoral artery catheter as necessary to reach and maintain a mean arterial blood pressure between 35 and 40 mm Hg. Intravenous fluid resuscitation commenced after two hours of hemorrhage or if mean arterial pressure fell below 30 mm Hg for ten minutes or 25 mm Hg for one minute.

Resuscitation. The goal of intravenous fluid resuscitation was to reach and maintain a mean arterial pressure above 75 mm Hg for three hours. An additional goal



in one-half of the rats in each fluid group was to reach and maintain a  $P_iCO_2 \leq 50$  mm Hg by administering one to two boluses of enalaprilat (0.06 mg/kg). The intravenously administered resuscitation fluids were as follows: (a) lactated Ringer's (LR) infused at 1 ml/min ( $n = 26$ ), (b) 6% dextran 70 mixed with lactated Ringer's solution (Dx) infused at 1 ml/min ( $n = 26$ ), or (c) 7.8% NaCl in 6% dextran 70 (HSD) infused at 1 ml/min followed by 6% dextran 70 mixed with lactated Ringer's also infused at 1 ml/min ( $n = 13$ ). The 6% dextran 70 mixed with lactated Ringer's solution was designed to replace interstitial fluid (3/7 lactated Ringer's) and intravascular volume (4/7 6% dextran 70). In the experiments in which 7.8% NaCl in 6% dextran 70 was used, the maximum volume of 7.8% NaCl administered was to be 4 ml/kg. Any additional fluid for maintenance of blood pressure would have been the 6% dextran 70 mixed with lactated Ringer's.

Assessments. *Cardiorespiratory status.* Mean arterial pressure was monitored continuously throughout the procedures. Hematocrit, total plasma protein, arterial  $PO_2$  ( $P_aO_2$ ), arterial  $PCO_2$  ( $P_aCO_2$ ), arterial pH ( $pH_a$ ), and arterial base excess were measured at the start of hemorrhage, at five minutes into resuscitation, and at 120 minutes into resuscitation. A blood sample was taken five minutes into resuscitation instead of at the start of resuscitation because the rats were unable to tolerate withdrawal of the one-half ml of blood required for blood-gas analysis at end-hemorrhage. In rats that died

before five minutes of resuscitation, a blood sample taken immediately after death was run for base excess. Total blood lost and volume of fluid returned were also assessed. *GI mucosal perfusion adequacy.* Colonic  $P_i\text{CO}_2$  was measured at 5-minute intervals throughout the procedures.

Statistical Analyses. Data were compared using ANOVA (Microsoft Excel software).

Power Analysis. Based on a power analysis, 20 animals were planned per resuscitation group; however, the hypertonic saline dextran arms of this study were terminated for 100% mortality after 13 rats and the other arms were halted because colonic  $P_i\text{CO}_2$  in these fasted rats did not have the predictive power for mortality that had been observed with non-fasted hemorrhaged and resuscitated rats.

## Results

Nine of the 74 rats died before resuscitation began. Of the remaining 65, apnea followed by a rapidly declining MAP and death occurred in 13 of 13 receiving 7.8% NaCl less than 1 minute ( $39 \pm 2$  sec) into resuscitation. Only 2 of 26 receiving lactated Ringer's died (1 min each into resuscitation), and only 3 of 26 receiving 6% dextran 70 died (30 sec, 1 min, and 10 min into resuscitation). At the start of resuscitation, there did not appear to be any significant differences between the rats that died and those that survived (Table 1). Since the rats receiving the hypertonic saline

dextran did not survive long enough, no five minute  $\text{pH}_a$  and base excess comparisons to survivors were possible.

## Discussion

Based on promising experimental and clinical results, hypertonic saline dextran solutions may well have a role to play in trauma resuscitation, especially when head trauma is involved.<sup>6,12,13</sup> The administration of hypertonic saline dextran solutions restores cardiac index and oxygen delivery more quickly than the administration of either non-hypertonic colloids or non-hypertonic crystalloids.<sup>1-3</sup> Hypertonic saline dextran has also been shown to better restore microvascular perfusion and decrease neutrophil/endothelial cell interactions during resuscitation than non-hypertonic solutions.<sup>4,5</sup>

The present study, however, offers a note of caution when using hypertonic saline dextran solutions for resuscitation from severe hemorrhagic shock. No differences were apparent at the start of resuscitation (Table 1) among rats that received hypertonic saline dextran and those that received either 6% dextran 70 mixed with lactated Ringer's or lactated Ringer's alone. Every rat that received hypertonic saline dextran, however, became apneic and died while the majority (90%) of the rats that received either 6% dextran 70 mixed with lactated Ringer's or lactated Ringer's alone survived resuscitation. The rate at which these fluids were

administered was relatively rapid (1 ml/min in a 300 gram rat would be equivalent to 233 ml/min in a 70 kg person) but certainly attainable in clinical practice. The results reported here, combined with the reports of respiratory depression in pigs<sup>1</sup> and sheep<sup>2</sup> receiving 4 ml/kg of hypertonic saline dextran over 4 minutes or less for resuscitation from shock, suggest that respiration should be closely monitored during hypertonic saline dextran resuscitation and that rapid hypertonic saline dextran administration should not be used unless the patient can be mechanically ventilated in the event of respiratory failure.

#### **Acknowledgements**

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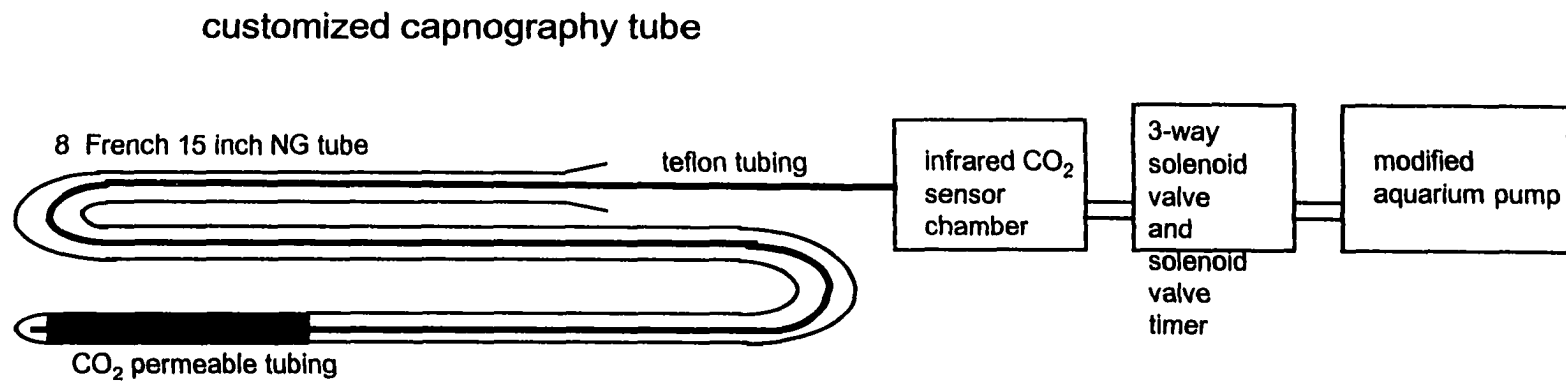


Figure 1. GI P<sub>i</sub>CO<sub>2</sub> monitoring system.

Table 1. Comparison of parameters in rats that died versus those that survived.

	died preR	HSD died	LR died	Dx died	LR surv	Dx surv
blood loss (ml/kg)	18 ± 3	19 ± 1	16 ± 2	24 ± 2	24 ± 1	25 ± 1
duration of H (min)	62 ± 12	93 ± 8	77 ± 17	77 ± 12	87 ± 5	80 ± 4
start R MAP (mmHg)	28 ± 1 <sup>a</sup>	25 ± 1	19 ± 2	20 ± 3	25 ± 1	26 ± 1
start R P <sub>i</sub> CO <sub>2</sub> (mm Hg)	65 ± 5 <sup>a</sup>	60 ± 2	64 ± 12	64 ± 5	61 ± 2	60 ± 2
5 min R pH <sub>a</sub>					7.15 ± .01	7.16 ± .01
dead pH <sub>a</sub>	6.99 ± .03	7.05 ± .02	7.02 ± .11	6.99 ± .07		
5 min R base excess					-14.2 ± .5	-13.4 ± .6
dead base excess	-18.0 ± 2.5	-19.0 ± .7	-17.9 ± 3.8	-19.6 ± 3.7		
IV fluid recieved (ml/kg)		2.6 ± .2	3.4 ± .1	17.6 ± 14.3	95 ± 11.8	23.2 ± 3.3

H = hemorrhage, R = resuscitation, MAP = mean arterial pressure

<sup>a</sup>last MAP and P<sub>i</sub>CO<sub>2</sub>



## GENERAL CONCLUSIONS

### General Discussion

Multiple organ dysfunction syndrome continues to develop in patients after episodes of hypovolemic shock, and elevations in gastrointestinal  $P_iCO_2$  continue to be associated with adverse patient outcomes, even in patients undergoing elective surgeries of only moderate risk.<sup>1</sup> The results contained in this dissertation highlight some important considerations in clinical shock resuscitation research, describe a monitoring system for measuring a variable believed to be related to outcome in a causal fashion, and discuss a hemorrhagic shock and resuscitation model.

Examining the use of different resuscitation fluids, the first paper illustrates the importance of good indicators of severity. The absence of differences in days in hospital and mortality in the two resuscitation groups cannot be solely attributed to a lack of difference in resuscitation fluids because the available indicators of clinical status of diarrheic calves may not be good indicators of disease severity or of risk for mortality.

In human patients, one indicator of morbidity and mortality risk from trauma or surgery is gastrointestinal  $P_iCO_2$ . How well this indicator crosses species has not been fully determined. Therefore, a relatively simple and inexpensive technique was devised for automated monitoring of gastrointestinal  $P_iCO_2$ . The use of this system in laboratory

models of hemorrhagic shock and resuscitation which result in inflammatory organ damage and in veterinary clinical diseases which model human clinical conditions will help determine if the relationship between an elevated gastrointestinal  $P_iCO_2$  and adverse outcomes is seen in other species. The ability to easily monitor gastrointestinal  $P_iCO_2$  will also be helpful in determining if a decreased gastrointestinal mucosal energy status truly plays a causal role in the initiation and potentiation of multiple organ dysfunction syndrome.

The development and use of a rat hemorrhagic shock and resuscitation model which causes considerable organ pathology and mortality allowed investigation of the relationship between gastrointestinal  $P_iCO_2$  and outcome. With no fasting, gastrointestinal  $P_iCO_2$  was associated with mortality in a manner similar to that reported in humans. With the addition of fasting before hemorrhage, several results worth noting occurred: 1)  $P_iCO_2$  no longer predicted outcome, 2) organ pathology and mortality worsened, and 3) hypertonic saline dextran, a clinically used resuscitation fluid, was found to cause apnea when administered at 4 ml/kg/minute. The clinical implications of these results are that respiration should be closely monitored when hypertonic saline dextran solutions are used and that the effects of pre-surgery fasting on patient morbidity and mortality risk and on the value of  $P_iCO_2$  monitoring should be evaluated.

### Recommendations for Future Research

How fasting affects the ability to detect important changes in gastrointestinal mucosal energy status and may also contribute to multiple organ dysfunction syndrome development are clinically important questions for two reasons. First, fasting is not uncommon in patients at risk for the development of multiple organ dysfunction syndrome. A fast of at least eight hours is common before any planned surgery involving general anesthesia, and enteral delivery of nutrients is commonly delayed for many hours or even days after surgery and after trauma resuscitation. Second, gastrointestinal  $P_iCO_2$  information has been shown to be predictive of outcome and is being incorporated into patient resuscitation algorithms.<sup>3,4</sup> Therefore, the relationships between fasting, gastrointestinal mucosal energy status, gastrointestinal  $P_iCO_2$ , and the events involved in the development of multiple organ dysfunction syndrome elucidation.

If gastrointestinal  $P_iCO_2$  is truly reflective of mucosal ATP hydrolysis unmatched by mitochondrial ATP resynthesis, the results observed in our fasted rats (Chapter 6) might be explained in several ways: 1) fasting protected mucosal ATP levels; 2) fasting uncoupled the association between unbalanced mucosal ATP hydrolysis and adverse outcome; or 3) fasting decreased the mucosal cellular mass or individual cellular ATP content to such an extent that  $H^+$  production from

ATP hydrolysis was markedly reduced and a higher  $P_iCO_2$  in this context represented a greater preservation of mucosal cells.

$^{31}P$  nuclear magnetic resonance spectroscopy may allow the determination of how closely an increasing  $P_iCO_2$  that is not caused by an increasing arterial  $PCO_2$  tracks a decreasing ATP to ADP ratio and which, if any, of the above three reasons accounted for the absence of a higher  $P_iCO_2$  in non-surviving fasted rats.

How pre-hemorrhage fasting predisposes to increased organ damage and mortality also needs to be determined. It is possible that fasting acts as a neutrophil priming stimulus even before hemorrhage or that fasting, by increasing gastrointestinal mucosal compromise, increased the priming and activation of neutrophils during hemorrhage and resuscitation. Since increased neutrophil expression of CD18 accompanies neutrophil priming, comparisons of neutrophil CD18 expression in fasted and non-fasted rats before and during hemorrhage and resuscitation should help determine how pre-fasting increases organ damage.

## References

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